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(54) Title: **A METHOD FOR TREATING HERPES VIRUSES**

(57) Abstract: The present invention relates to a method for selecting an anti-herpes viral compound and a method for selectively inhibiting herpesvirus in a human host in need of such treatment. The present invention relates to a method for selecting an anti-herpes viral compound and a method for selectively inhibiting herpesvirus in a human host in need of such treatment.

A METHOD FOR TREATING HERPES VIRUSES

FIELD OF THE INVENTION

The present invention relates to a method for selecting an anti-herpes viral
5 compound and a method for selectively inhibiting herpes viruses in a human host in need of such treatment.

BACKGROUND OF THE INVENTION

The herpesviruses comprise a large family of double stranded DNA viruses. Eight
10 of the herpes viruses, herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella zoster virus (VZV), human cytomegalovirus (HCMV), Epstein-Barr virus (EBV), and human herpes viruses 6, 7, and 8 (HHV-6, HHV-7, and HHV-8), have been shown to infect humans. Several of these viruses are important human pathogens.

HSV-1 is estimated to affect 100 million people in the U.S. Primary infection of
15 HSV-1 usually occurs between the ages of one and four. Cold sores, the visible symptom, typically appear at a later age, with 20-45% of the population over the age of fifteen affected (Whitley, Clin. Infect. Dis., 26:541-555, 1998).

Genital herpes (HSV-2) is the second most common sexually transmitted disease, with approximately 22% of the U.S population infected with this virus (Fleming 1997).

20 VZV is the causative agent of chicken pox upon primary infection and can recur in adults as zoster.

EBV results in approximately two million cases of infectious mononucleosis in the U.S. each year. It can also cause lymphomas in immunocompromised patients and has been associated with Burkitt's lymphoma, nasopharyngeal carcinoma, and Hodgkins disease.

25 Infection with HCMV often occurs during childhood and is typically asymptomatic except in immunocompromised patients where it causes significant morbidity and mortality.

HHV-6 is the causative agent of roseola and may be associated with multiple sclerosis and chronic fatigue syndrome. HHV-7 disease association is unclear, but it may
30 be involved in some cases of roseola. HHV-8 has been associated with Kaposi's sarcoma, body cavity based lymphomas, and multiple myeloma.

These viruses are capable of residing in a latent state within the host. Reactivation of latent virus results from response to environmental stimuli (ex. UV exposure, stress,

etc.). Infections or recurrence can be life threatening in immunocompromised patients such as AIDS or transplant patients where HCMV can result in retinitis, pneumonia, and gastrointestinal disease.

The increased immunocompromised population has created an unmet medical need
5 for antivirals against herpesviruses because current therapies do not have a sufficiently broad spectrum against this family of viruses and/or they have limited utility due to toxicity. The present invention provides a method for selectively inhibiting herpesviruses DNA polymerase with compounds that have broad spectrum activity. The method offers a distinct advantage in the treatment of patients in need, particularly immunocompromised
10 patients at risk of infection or reactivation by many members of the herpesvirus family.

SUMMARY OF THE INVENTION

The present invention provides a method of selecting compounds that inhibit herpes viruses comprising:

- 15 a) measuring IC_{50} of a compound of interest that inhibits a wild type herpes virus,
- b) measuring IC_{50} of the same compound that inhibits a binding domain mutant herpes virus which is the same strain of the wild type herpes virus,
- c) comparing IC_{50} of step a with IC_{50} of step b; and
- d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times
20 greater than the IC_{50} of step a.

In above method, the order of step a and step b are interchangeable.

The present invention further provides a method of selecting compounds that inhibit herpes viruses comprising:

- a) measuring IC_{50} of a compound of interest that inhibits a wild type HSV-1,
- 25 b) measuring IC_{50} of the same compound that inhibits a binding domain mutant HSV-1 which is the same strain of the wild type herpes virus,
- c) comparing IC_{50} of step a with IC_{50} of step b; and
- d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times
greater than the IC_{50} of step a.

30 In above method, the order of step a and step b are interchangeable.

The present invention further provides a method of selecting compounds that inhibit herpes viruses comprising:

- a) measuring IC_{50} of a compound of interest that inhibits a wild type HSV-2,

- b) measuring IC_{50} of the same compound that inhibits a binding domain mutant HSV-2 which is the same strain of the wild type herpes virus,
- c) comparing IC_{50} of step a with IC_{50} of step b; and
- d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.

In above method, the order of step a and step b are interchangeable.

The present invention further provides a method of selecting compounds that inhibit herpes viruses comprising:

- a) measuring IC_{50} of a compound of interest that inhibits a wild type HCMV,
- b) measuring IC_{50} of the same compound that inhibits a binding domain mutant HCMV which is the same strain of the wild type herpes virus,
- c) comparing IC_{50} of step a with IC_{50} of step b; and
- d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.

In above method, the order of step a and step b are interchangeable.

The present invention further provides a method for selectively treating diseases caused by herpes viruses in a human host comprising administering a compound to a human in need of such treatment wherein said compound inhibits herpes viruses by interaction with the binding domain in the viral DNA polymerase.

The present invention further provides method for selectively inhibiting herpes viruses in a human host comprising administering a compound to a human in need of such treatment wherein IC_{50} of the compound that inhibits a binding domain mutant herpes virus is at least 3 times greater than IC_{50} of the compound that inhibits a wild type herpes virus which is the same strain as the mutant herpes virus.

The present invention further provides a compound for treating herpesviral infections in a human host wherein IC_{50} of the compound that inhibits a binding domain mutant herpes virus is at least 5 times greater than IC_{50} of the compound that inhibits a wild type herpes virus which is the same strain as the mutant herpes virus.

The present invention further provides a compound for treating herpesviral infections in a human host wherein said compound inhibits the herpesvirus by interacting with the binding domain in the viral DNA polymerase.

The present invention further provides a compound for the inhibiting of herpesvirus DNA polymerases wherein serial passage of a wild type herpes virus in the presence of said

compound results in a change of the wild type HSV-1 polymerase at amino acid 823 from valine to alanine.

The present invention further provides a compound for inhibiting herpesvirus DNA polymerases wherein serial passage of a wild type herpes virus in the presence of said
5 compound results a change of the wild type HCMV polymerase at amino acid 823 from valine to alanine and at amino acid 824 from valine to leucine.

The present invention further provides a mutant herpesvirus DNA molecule having a nucleotide sequence selected from a group consisting of SEQ.ID.NO. 1; SEQ.ID.NO. 3; SEQ.ID.NO. 5; SEQ.ID.NO. 7; SEQ.ID.NO. 9; and SEQ.ID.NO. 11.

10 The present invention further provides a mutant herpesvirus polymerase amino acid molecule having an amino acid sequence selected from a group consisting of SEQ.ID.NO. 2; SEQ.ID.NO. 4; SEQ.ID.NO. 6; SEQ.ID.NO. 8; SEQ.ID.NO. 10 and SEQ.ID.NO. 12.

BRIEF DESCRIPTION OF THE DRAWINGS

15 Figure 1 – examples of 4-oxo-DHQ and 4-oxo-DHTP compounds.

Figure 2 – Herpesvirus' polymerases amino acid conserved region.

Figure 3 – Recovered virus after serial passage of HSV-1 in presence of 20 μ M of compound No. 17.

Figure 4 – Comparision of Wild HSV-1 and HSV-2 herpesvirus DNA polymerase
20 amino acid sequences alligned by amino acid homology. (Seq. No: 14-19)

Figure 5 – Mutant Herpes Virus DNA and amino acid sequence list. (Seq. No: 1-12)

Figure 6 – Wild HCMV herpesvirus DNA polymerases amino acid sequence. (Seq. No 13)

25 DETAILED DESCRIPTION OF THE INVENTION

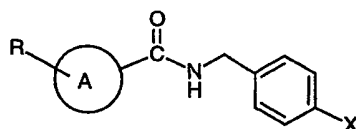
A key enzyme in the replication of all herpesviruses is the virus-coded DNA polymerase. Most of the currently available anti-herpes drugs target the viral DNA polymerase. Drugs such as Foscarnet acts by direct inhibition of the viral polymerase. These drugs are non-nucleoside inhibitors of herpesvirus DNA polymerases. Others such as the
30 nucleoside analogs, Acyclovir, Penciclovir and Ganciclovir must first be phosphorylated to the monophosphate forms by virus encoded kinases and, further phosphorylated to triphosphate by cellular enzymes before they are active inhibitors. The triphosphate forms of these nucleoside analogs inhibit polymerases by competing with the binding of natural

triphosphates and their subsequent insertion into growing DNA strands. These drugs are known as nucleoside inhibitors of herpesvirus DNA polymerases.

One of the limitations of the currently available drugs is that they are active against only a few of the eight human herpesviruses. For example, Acyclovir and Penciclovir
5 inhibit HSV and VZV replication but have poor activity against CMV.

In order to identify antiviral compounds that would have the potential to inhibit replication of most of the human herpesviruses, compounds are *in vitro* screened for inhibitors of herpesvirus DNA polymerase activity. Because portions of the amino acid sequence of the polymerases are highly conserved within the herpesvirus family it is
10 possible to discover small molecules that inhibit herpesvirus polymerases but not cellular DNA polymerases. Using this biochemical approach, several new classes of compounds such as the 4-hydroxyquinoline derivatives (4-HQ), 4-oxo-dihydroquinoline derivatives (4-oxo-DHQ) and 4-oxo-dihydrothienopyridine derivatives (4-oxo-DHTP) were discovered as potent, non-nucleoside herpesvirus DNA polymerase inhibitors. *In vitro* polymerase assays
15 and/or *in vivo* cell culture assays have demonstrated that these compounds inhibit HSV-1, HSV-2, HCMV, VZV, EBV, and HHV-8 replication.

4-Oxo-DHQ and 4-oxo-DHTP are derivatives of formula I



I

20 wherein ring A is a saturated or unsaturated fused double or triple heterocyclic ring having 1, 2, 3 or 4 heteroatoms selected from group consisting of oxygen, sulfur, or nitrogen; and wherein R and X are the appropriated substituents, respectively.

Examples of 4-HQ compounds, 4-oxo-DHQ compounds and 4-oxo-DHTP compounds are illustrated in **Figure 1**.

25 Antiviral activity of these examples are shown in Table 1 below. As shown in Table 1, these compounds inhibit HSV-1 and HSV-2 as well or better than the current commercially available drug Acyclovir.

Table 1
Antiviral Activity of 4-oxo DHQ/4-oxo DTHP Against HSV-1 and HSV-2

virus	Compound IC ₅₀ (uM)					ACV
	1	2	3	4	5	
HSV-1 KOS	2.0	3.8	3.2	3.2	3.3	3.6
HSV-1 F	2.5	2.3	2.2	2.1	2.6	1.3
HSV-1 DJL	2.5	2.6	1.8	2.2	2.7	1.8
HSV-1 Patton	ND	5.3	7.7	4.3	10	9.3
HSV-2 MS	2.0	2.5	2.8	2.5	2.5	10
HSV-2 35D	ND	5.4	5.0	3.2	8.1	6.0
HSV-2 186	2.0	2.3	3.2	2.3	4.2	>10

5 It has also been discovered that point mutations within the HSV-1 polymerase gene that confer resistance to Acyclovir and other nucleoside analogs do not result in resistance to the 4-HQ, 4-oxo-DHQs or 4-oxo-DHTPs. Serial passage of wild type HSV-1 in the presence of 4-oxo-DHQ results in the isolation of mutants that are highly resistant (>20 fold increase in the IC₅₀) to these compounds while retaining sensitivity to nucleoside inhibitors
 10 such as Acyclovir.

In order to determine the mechanism of action of 4-HQ, 4-oxo-DHQ and 4-oxo-DHTP compounds against herpes viruses, mutants resistant to these compounds are isolated by serial passage of the virus in the presence of a 4-oxo-DHQ compound. Sequencing analysis of HSV-1 and HSV-2 strains resistant to the 4-oxo-DHQ identifies that HSV-1
 15 (KOS strain) polymerase protein and its homologous HSV-2 have a conserved region (a binding domain), which is a critical contact point for these compounds. While amino acid numbering of the DNA polymerase may vary between strains of HSV-1 and HSV-2, this binding domain encompassing the HSV-1 (KOS) strain amino acid 823 is highly conserved in herpesviruses and can be identified by aligning the homologous amino acids of this
 20 domain as shown in Fig 2.

In HSV-1 and HSV-2 strains resistant to the 4-oxo-DHQ and similar compounds, a change of valine to an alanine at the binding domain provides full resistance.

In the HSV-1 DNA polymerase, resistance is also found when a valine changes to methionine at amino acid 823 but only when accompanied by a second amino acid change.

25 Isolation of HCMV resistant to 4-oxo-DHQ's is found to be very difficult. Comparison of the amino acid sequence of the HSV polymerase (Y-G-F-T-G-V-Q-H-G) and HCMV polymerase (Y-G-F-T-G-V-V-N-G) in the region of amino acid 823 (underlined amino acid) shows that there is a second valine at position 824 in the HCMV

polymerase. In vitro assay using mutant HCMV polymerases demonstrates that full resistance to the 4-oxo-DHQs requires changes at both amino acids 823 (a valine to alanine) and 824 (a valine to leucine). A HCMV polymerase gene containing V823A and V824L mutations is used in marker rescue experiments to generate a viral mutant. This mutant has
5 an IC₅₀ approximately 7-fold above that of wild-type HCMV.

The HSV-1, HSV-2 and HCMV mutants are also found to be resistant to other non-nucleoside inhibitors such as the 4-oxo-DHTP and similar compounds. However, when the binding domain mutants (e. g. HSV-1 V823A, HSV-2-MS V826A, HSV-2-186 V828A, and HCMV V823A/V824L mutants) are tested in plaque reduction assays against a series of
10 nucleoside polymerase inhibitors and the non-nucleoside inhibitor such as Foscarnet, replication of the mutants is found to be inhibited by all of the currently marketed anti-herpes polymerase inhibitors tested.

These studies demonstrate that certain non-nucleosides like 4-HQ, 4-oxo-DHQ and 4-oxo-DHTP compounds bind to a different site on the herpes polymerase than the
15 nucleoside inhibitors and Foscarnet. The valine at the binding domain is conserved in the DNA polymerases of six of the eight human herpesviruses and several animal herpesviruses, and appears to play a critical role in the antiviral activity of the 4-HQ, 4-oxo-DHQ and 4-oxo-DHTP compounds. (See Figure 2)

Since mutation at the binding domain negates these non-nucleoside inhibitors' activities, compounds could be tested against wild type polymerases and the mutant
20 polymerases to establish the probability of similar binding. We refer to this property of compounds as interaction with the binding domain. Since compounds that interact with the binding domain have exhibited broad-spectrum activity against herpesviruses, this invention provides a method for selecting compounds to treat individuals such as
25 immunocompromised patients who are afflicted with multiple herpesvirus infections.

Definitions

The term " wild-type" refers to a gene or gene product which has the characteristics of that gene or gene product when isolated from a naturally occurring source. A wild-type
30 gene is that which is most frequently observed in a population and is thus arbitrarily designated the "normal" or " wild-type" form of the gene.

In contrast, the term "mutant" refers to a gene or gene product which displays modifications in sequence and or functional properties (i.e., altered characteristics) when

compared to the wild-type gene or gene product. It is noted that naturally-occurring mutants can be isolated; these are identified by the fact that they have altered characteristics when compared to the wild-type gene or gene product.

IC₅₀ refers to concentration of a drug that inhibits virus growth by 50%.

5 Wild type HSV-1 and HSV-2 strains are listed in Figure 4.

Wild type HCMV is listed in SEQ. ID. NO.13.

The term "Iudr" refers to antiviral drug Iododeoxyuridine.

The term "Bvdu" refers to antiviral drug Bromovinyldeoxyuridine.

The term "ACV" refers to antiviral drug Acyclovir.

10 The term "AraC" refers to antiviral drug Arabinosylcytidine.

The term "AraT" refers to antiviral drug Arabinosylthymine.

The term "AraA" refers to antiviral drug Arabinosyladenine.

The term "GCV" refers to antiviral drug Ganciclovir.

The term "CDV" refers to antiviral drug Cidofovir.

15 The term "PFA" refers to antiviral drug Foscarnet.

The term "binding domain" refers to a conserved region in herpesvirus DNA polymerases. The herpesvirus DNA polymerases have seven (7) conserved regions. The binding domain is within the third conserved region (see Figure 2). When the binding domain contacts with an inhibitor, at least one amino acid in the binding domain mutates and provides the resistance. In general, the binding domain is at an amino acid sequence position 818-829 of the HSV-1 DNA polymerase or the homologous region in other herpes virus DNA polymerases (see Figure 2).

The term "a binding domain mutant herpes virus" refers to a herpes virus containing a binding domain mutation.

25 More specifically, the binding domain in HSV-1 strains, KOS, F, DJL and Patton are at amino acid sequence position 823. The binding domain in HSV-2 MS-M1 strain is at amino acid sequence position 826. The binding domain in HSV-2 186 strain is at amino acid sequence position 828. The binding domain in HCMV AD 169 strains is at amino acid sequence position 823-824.

30 The term "XxxxY" refers to an amino acid sequence position xxx, a single amino acid X in wild type is changed to an amino acid Y.

For example, the term "V823A" refers to an amino acid sequence position 823, a Valine found in wild type is changed to alanine in mutant strain.

The term "V824L" refers to an amino acid sequence position 824, a Valine found in wild type is changed to Leucine in mutant strain.

The term "V826A" refers to an amino acid sequence position 826, a Valine found in wild type is change to alanine in mutant strain.

- 5 The term "V828A" refers to an amino acid sequence position 828, a Valine found in wild type is change to alanine in mutant strain.

A table of amino acids and their representative abbreviations, symbols and codons is set forth below in the following Table.

10

Amino acid	Abbrev.	Symbol	Codon(s)					
Alanine	Ala	A	GCA	GCC	GCG	GCU		
Cysteine	Cys	C	UGC	UGU				
Aspartic acid	Asp	D	GAC	GAU				
Glutamic acid	Glu	E	GAA	GAG				
Phenylalanine	Phe	F	UUC	UUU				
Glycine	Gly	G	GGA	GGC	GGG	GGU		
Histidine	His	H	CAC	CAU				
Isoleucine	Ile	I	AUA	AUC	AUU			
Lysine	Lys	K	AAA	AAG				
Leucine	Leu	L	UUA	UUG	CUA	CUC	CUG	CUU
Methionine	Met	M	AUG					
Asparagine	Asn	N	AAC	AAU				
Proline	Pro	P	CCA	CCC	CCG	CCU		
Glutamine	Gln	Q	CAA	CAG				
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU
Threonine	Thr	T	ACA	ACC	ACG	ACU		
Valine	Val	V	GUA	GUC	GUG	GUU		
Tryptophan	Trp	W	UGG					
Tyrosine	Tyr	Y	UAC	UAU				

MATERIALS AND METHODS

Cell and Viruses

- African green monkey kidney cells (Vero) and human foreskin fibroblast cells (HFF) and herpes viruses can be obtained from the American Type Culture Collection (ATCC). Media is defined as Dulbecco's modified Eagle media (DMEM) containing 10% fetal bovine serum (FBS) and supplemented with antibiotics. Cells are maintained in media at 37°C in a humidified atmosphere of 5% CO₂. HSV-1 strains F, Patton and DJL, HSV-2 strains MS, 35D and 186, and HCMV strain AD169 are used in these studies. Strain DJL is a clinical isolate of HSV-1 isolated in our lab from a primary oral lesion.
- 15
- 20

Measuring IC₅₀ of a Compound of Interest That Inhibits Herpes Viruses

Preparation of Virus Stocks: HSV-1 and HSV-2 stocks are grown in Vero cells.

HCMV stocks are grown in HFF cells. Approximately 1 ml of media containing sufficient

virus to infect approximately 0.1% to 1% of the cells (multiplicity of infection of 0.001 to

5 0.01 PFU/cell) is added to a T-150 cell culture flask containing a confluent monolayer of

cells. The cells are incubated at 37°C for approximately 1 hour. Approximately 50 ml of

media is then added to the flask and the cells are incubated at 37°C until viral cytopathic

effect (cpe) is apparent in 100% of the cells. The flask is then placed at -80°C for at least

30 min. The flask containing frozen media and cells is placed in a 37°C water bath until the

10 media is thawed. This process disrupts the cells and releases virus into the media. 1 ml

aliquots of media containing virus are dispensed into tubes and stored at -80°C. These

aliquots of media containing virus are referred to as virus stocks.

Titration Virus Stocks: Aliquots of virus are thawed at 37°C and serially diluted (10

fold dilutions) in media. 0.1 ml of each dilution of virus is placed in a single well of 24-

15 well cell culture dish containing a confluent monolayer of cells (Vero cells for HSV-1 and

HSV-2, HFF cells for HCMV) and incubated at 37°C for 1 h. The virus inoculum is then

removed and 1 ml of media containing 0.8% carboxymethylcellulose (CMC) is added to

each well of the dish. The dish is incubated at 37°C for approximately 2-3 days (HSV-1

and HSV-2) or 6-9 days (HCMV) to allow sufficient growth of virus to form plaques in the

20 cell monolayer. Plaques can be observed and counted microscopically or by staining the

cells with 0.1% crystal violet in 20% ethanol. The virus titer which is expressed as plaque

forming units (PFU) per ml is obtained by counting the plaques in a well and correcting for

the dilution of the viral inoculum.

Plaque Reduction Assays: Antiviral activity of compounds against herpesviruses such as

25 HSV-1, HSV-2, or HCMV can be measured using plaque reduction assays. 0.1 ml of media

containing approximately 50 PFU of virus is added to each well of a 24-well cell culture

dish containing a confluent monolayer of cells (Vero cells for HSV-1 and HSV-2, HFF cells

for HCMV). Compounds are dissolved in 100% DMSO and diluted in 100% DMSO as

200x stocks of the desired final drug concentration. Typically 5-6 two-fold dilutions are

30 prepared for each compound. Dilutions of compounds are then added to media containing

0.8% CMC resulting in a final 1x drug concentration. After the virus-infected cells have

incubated for 1 h at 37°C, the virus inoculum is removed and 1 ml of media containing

0.8% CMC and the various concentrations of compound is added to each well of the dish.

The dish is incubated at 37°C for approximately 2-3 days (HSV-1 and HSV-2) or 6-9 days (HCMV) to allow sufficient growth of virus to form plaques in the cell monolayer. Plaques can be observed and counted microscopically or by staining the cells with 0.1% crystal violet in 20% ethanol. Virus inhibition is determined for each drug concentration by
5 comparing the number of plaques in drug-containing wells to control wells that did not contain drug. Antiviral activity of a compound is expressed as the concentration of compound predicted to reduce the number of plaques in a well by 50% (IC₅₀). The IC₅₀ values are calculated by plotting the per cent inhibition vs. concentration of compound using EXCEL software for linear regression.

10

Selection of 4-oxo-DHQ resistant HSV-1 and HSV-2

Vero cells are plated out at a density of 3.5×10^5 cells per well in a six well tissue culture plate. Cells are infected with HSV-1 KOS at a multiplicity of infection (moi) of 0.1 pfu/cell and 1 h post infection the cells are overlaid with 3 ml media containing 20
15 uM of a 4-oxo-DHQ. Cultures are incubated for 20 h at 37°C, freeze/thawed to release cell-associated virus, and 0.1 ml of culture is used to infect a new monolayer of Vero cells (one passage). Serial passage is repeated seven times in the presence of 20 uM drug. Virus isolates are then plaque purified three times prior to preparation of stocks. Virus recovered from each passage in the presence of compound No. 17 is shown in Figure 3. 4-oxo-DHQ
20 resistant HSV-1 and HSV-2 may also be selected by the marker transfer method described below using wild-type HSV DNA and the corresponding mutant HSV polymerase gene.

Marker Transfer of a HCMV Mutation

A plasmid containing the wild-type HCMV polymerase gene is modified to contain
25 the V823A or V823A and V824L mutations using a site-directed mutagenesis Kit (Stratagene Corp.) and following the manufactures's protocol. HFF cells are plated into T25 tissue culture flasks to achieve 80% confluency at the time of the transfection. Wild type HCMV AD169 DNA and plasmid DNA containing the mutant HCMV polymerase gene are mixed at a ratio of 1:2 (2ug of viral DNA to 4 ug of plasmid DNA). DNA's are
30 transfected using superfect transfection reagent according to methods recommended by the manufacturer (Quiagen Inc.). Cells are harvested five days posttransfection, freeze-thawed to release virus and half of the sample is used to infect HFF cell monolayers. Cells are overlaid with media containing 20 uM 4-oxo-DHQ compound 2 (see Figure 1). Serial

passage is repeated seven times in the presence of 20 uM compound 2 and virus isolates are then plaque purified three times prior to preparation of viral stock.

Isolation of HSV and HCMV viral DNA

5 HSV DNA is purified from the cytoplasm of infected Vero cells. Vero cells (50 % confluent) are infected at an multiplicity of 0.01 PFU/cell. At 3-5 days postinfection infected cells (100% cpe) are harvested by centrifugation at 1000 rpm in a Beckman GS-6R centrifuge. The pelleted cells are resuspended in TE buffer and placed on ice for 15 minutes. NP-40 is then added to a final concentration of 0.2% and incubated on ice for a
10 further 15 minutes. The cells are centrifuged at 2000 rpm for 10 minutes in a Beckman GS-6R centrifuge. The supernatant is removed and EDTA is added to a final concentration of 20 mM followed by the addition of SDS to a final concentration of 0.3% and proteinase K to a concentration of 50 ug/ml then incubated at 45C for 2 hours. HCMV DNA is isolated by infecting HFF cells (25% confluency) with HCMV at an multiplicity of 0.1 PFU/cell.
15 Cells and media are harvested 5-7 days postinfection (100% cpe) and subjected to low speed centrifugation to remove intact cells and cell debris followed by a high speed spin to pellet virus particles (2500 rpm's in a Beckman SW28 rotor for 1 hour). Following incubation of the HSV and HCMV samples, 1.5 volumes of saturated NaI is added to the digested extract and the refractive index is adjusted to 1.434 –1.435. Ethidium bromide is
20 added to a final concentration of 50 ug/ml. The samples are loaded into a VTI 50centrifuge tube and spun for 24 hours at 45,000 rpm. The DNA band is harvested extracted three times with n-butanol, then dialyzed against TE buffer followed by a dialysis against 95% ethanol and a final dialysis against TE buffer.

DNA Sequencing

25 HSV-1, HSV-2 or HCMV viral DNA's are sequenced directly using an ABI377 fluorescence sequencer (Perkin Elmer Applied Biosystems, Foster City, CA) and the ABI BigDye PRISMTM dRhodamine Terminator Cycle Sequencing Ready Reaction Kit with AmpliTaq FSTM DNA polymerase (PE Applied Biosystems). Each cycle sequencing
30 reaction contained about 1.0 ug of purified viral DNA. Cycle-sequencing is performed using an initial denaturation at 98°C for 1 min, followed by 50 cycles: 98°C for 30 sec, annealing at 50°C for 30 sec, and extension at 60°C for 4 min. Temperature cycles and times are controlled by a Perkin-Elmer 9700 thermocycler. Extension products are

purified using Centriflex™ gel filtration cartridges (Edge BioSystems, Gaithersburg, MD). Each reaction product is loaded by pipette onto the column, which is then centrifuged in a swinging bucket centrifuge (Sorvall model RT6000B table top centrifuge) at 750 x g for 1.5 min at room temperature. Column-purified samples are dried under vacuum for about 40 min and then dissolved in 4 ul of a DNA loading solution (83% deionized formamide, 8.3 mM EDTA, and 1.6 mg/ml Blue Dextran). The samples are then heated to 90°C for two min, and held at 4°C until loading. 1.5 ul of each sample is loaded into a single well of the ABI377 sequencer. Sequence chromatogram data files from the ABI377 are analyzed with the computer program Sequencher (Gene Codes, Ann Arbor, MI), for assembly of sequence fragments and correction of ambiguous base calls. Generally sequence reads of 600-700 bp are obtained. Potential sequencing errors are minimized by obtaining sequence information from both DNA strands and by re-sequencing difficult areas using primers at different locations until all sequencing ambiguities are removed.

The entire coding region of the polymerase genes from both the parent strains and the resistant viruses are sequenced. The DNA sequencing is done using viral DNA as the template thus avoiding cloning of the polymerase genes. The amino acid sequence of the DNA polymerases of HSV-1 KOS, F, Patton and DJL and HSV-2 MS and 186 are compared in Figure 4. Amino acids that are identical for the six polymerases are shaded in black while regions where amino acid differences are found are shaded in gray. The amino acid sequence of the four HSV-1 polymerases are essentially identical with only a few minor changes noted between the different HSV-1 strains. The majority of amino acid changes are found when the sequences of the HSV-1 and HSV-2 polymerases are compared.

Isolation and Characterization of HSV-1 and HSV-2 Mutants That Are Resistant To the 4-oxo-DHQ's and 4-oxo-DHTP Compounds

A panel of viruses consisting of four strains of HSV-1 (KOS, F, DJL, Patton) and three strains of HSV-2 (MS, 35D, 186) are tested in a plaque reduction assay against four different 4-oxo-DHQ compounds (# 1, 2, 4, 5 as shown in Figure 1), and one 4-oxo-DHTP compound (# 3 as shown in Figure 1) and against Acyclovir. The six drugs inhibited replication of the seven virus strains with IC₅₀ values ranging from 2-10 µM (Table 1). In order to select for 4-oxo-DHQ resistant mutants, HSV-1 strains KOS, F, and DJL along with HSV-2 strains 186 and MS are serially passaged in the presence of 20 µM compound

1. Following the seventh passage, 4-oxo-DHQ resistant virus from each strain are plaque purified three times and high-titer stocks are made. All of the resistant HSV mutants grew to high titers in Vero cells, indicating that the mutations in the resistant isolates did not significantly impair their growth. The mutants selected with 4-oxo-DHQ compound 1 exhibited >10 fold increase in IC₅₀ when tested in a plaque reduction assay against 4-oxo-DHQ compound 1 Data are shown in Table 2.

Table 2

4-oxo-DHQ Resistant Virus of HSV-1 and HSV-2

Virus Mutants	Compound 1 IC₅₀ (uM)	Amino Acid Change in HSV DNA Polymerase
HSV-1 Kos-M1	>20	- V823A
HSV-1 F-M1	>20	- V823A
HSV-1 DJL-M1	>20	-V823A
HSV-2 MS-M1	>20	- V826A
HSV-2 186-M1	>20	- V828A

- *HSV-1 and HSV-2 isolates grown in the presence of 4-oxo-DHQ select for resistant virus.

DNA sequence analysis of the 4-oxo-DHQ resistant mutants (HSV-1 KOS-M1, HSV-1 F-M1, HSV-1 DJL-M1, HSV-2 186-M1, HSV-2 MS-M1) demonstrated that all five mutants contained a single point mutation of T to C at the binding domain resulting in a Valine to Alanine amino acid change.

Isolation and Characterization of A HCMV Mutant That Is Resistant to The 4-oxo-DHQ's and 4-oxo-DHTP Compounds

- In order to select for a 4-oxo-DHQ HCMV resistant mutant, virus (strain AD169) is serially passaged in the presence of 20 uM a 4-oxo-DHQ. Although we could readily select for HSV mutants using this procedure we failed to isolate an HCMV mutant, even when the virus is passaged at low drug concentrations (<5 uM). Comparison of the amino acid sequence of the HSV polymerase, Y-G-F-T-G-V-Q-H-G, and HCMV polymerase, Y-G-F-T-G-V-V-N-G, in the region of amino acid 823 (underlined amino acid) showed that there is a second valine at position 824 in the HCMV polymerase. In order to determine if both valines need to be changed in order to confer resistance to the 4-oxo-DHQ's, *in vitro* polymerase assays are done using mutant HCMV polymerases containing either V823A or V823A plus V824L (Table 3).

Table 3
HCMV Mutant Polymerase Exhibits Resistance to 4-oxo-DHQ*

Polymerase	Compound 1 IC ₅₀ (uM)
HCMV (wild)	4.6
HCMV V823A	17.2
HCMV V823A/V824L	42.9

*Generation of the valine to alanine at amino acid 823 of HCMV results in a 3.5-fold increase in resistance.

*Mutation of the amino acid from valine to alanine and amino acid 824 from valine to leucine results in an 9-fold increase in resistance, relative to wild type.

The V823A alone resulted in a 3.5-fold increase in the IC₅₀ while the polymerase with the double amino acid change had nearly 10-fold increase in the IC₅₀. In order to isolate an HCMV resistant mutant marker rescue experiments are done. Plasmids containing the mutant polymerase genes are transfected into HFF cells along with wild type HCMV AD169 DNA. The resulting virus is then serially passaged in the presence of 20 uM compound 1 (see figure 1). A 4-oxo-DHQ resistant virus is isolated from marker rescue studies done with the HCMV polymerase gene containing mutations that result in the V823A, V824L amino acid changes, but not with the gene containing V823A change alone. The mutant selected with compound 1 (HCMV AD169-M1) exhibited ~7-fold increase in IC₅₀ when tested in a plaque reduction assay compared to Ganciclovir and cidofovir which has a \leq 2-fold change in sensitivity (Table 4).

Table 4
Plaque reduction assay of 4-oxo-DHQ resistant HCMV*

Drug	HCMV AD169 IC ₅₀ (uM)	HCMV AD169 – M1 IC ₅₀ (uM)
Compound 1	0.7	4.7
Ganciclovir	0.9	1.0
Cidofovir	0.3	0.6

*Recombination of wild-type HCMV with a polymerase gene containing the valine to alanine at amino acid 823 and the valine to leucine at amino acid 824 allowed for selection of resistant virus with about 7-fold less sensitivity to compound 1.

*Sensitivity of resistant HCMV virus to Ganciclovir and Cidofovir verifies that the 4-oxo-DHQ's mechanism for inhibiting the polymerase protein is unique

The entire coding region of the HCMV polymerase genes from both the parent strain and the resistant virus are sequenced. The DNA sequencing is again done using viral DNA as the template thus avoiding cloning of the polymerase genes. Comparison of the DNA sequence of the two polymerase genes demonstrated that the resistant mutant
5 contained two point mutations that resulted in the predicted V823A, V824L amino acid changes. As with the HSV resistant viruses these results demonstrate the critical role of the region encompassing amino acid 823 for inhibition of polymerase activity by these compounds.

10 **Antiviral Activity of Nucleoside and Non-Nucleoside Polymerase Inhibitors Against 4-oxo-DHQ Resistant Mutants**

In order to determine if the 4-HQ binding domain mutations alter the sensitivity of the HSV-1, HSV-2 and HCMV mutants to both non-nucleoside (4-oxo-DHQ's) and nucleoside inhibitors (e.g Acyclovir and ganciclovir) several of the mutants are tested in
15 plaque reduction assays against a series of non-nucleoside compounds including Foscarnet (PFA), 4-HQ's 4-oxo-DHQ's and 4-oxo-DHTP's (Table 5). The mutants are also tested against a series of nucleoside inhibitors including acyclovir and ganciclovir (Table 5). The activity of these compounds against the mutants is compared to their activity against the wild type strains that are used to isolate the HSV and HCMV mutants. When tested against
20 a number of 4-HQ's, 4-oxo-DHQ's and 4-oxo-DHTP's and other related classes of compounds all of the drugs are found to inhibit the wild type virus with IC_{50} values ranging from $<0.1 \mu M$ to $30 \mu M$. When these drugs are tested against the resistant viruses they are found to have IC_{50} values 5 to 10 fold higher than the parent virus. There is little if any difference in the IC_{50} values of the nucleoside compounds and the non-nucleoside PFA
25 between the wild type and mutant HSV-1, HSV-2, and HCMV viruses. These results demonstrate that the amino acid change in the binding domain (V823A in the HSV-1 polymerase, V826A in the HSV2-MS polymerase, V828A in the HSV2-186 polymerase, and the V823A/V824L changes in the HCMV polymerase) resulted in resistance to the 4-oxo-DHQ's and 4-oxo-DHTP's, which provides further evidence that these classes of
30 compounds share an affinity for a region we refer to as the binding domain. In contrast, these amino acid changes did not alter the activity of these viruses to other classes of polymerase inhibitors.

Table 5

Antiviral activity of nucleoside and non-nucleoside polymerase inhibitors
against HSV-1, HSV-2, and HCMV Isolates selected for 4-oxo-DHQ resistance*

Drug	Plaque Reduction Assay – IC ₅₀ (μM)					
	HSV-2 MS	HSV-2 MS-M1	HSV-1 KOS	HSV-1 KOS-M1	HCMV AD169	HCMV AD169-M1
6	28.8	>50	24.6	>50	5.1	>16
7	8.8	27.9	6.5	>50	0.3	3.4
8	2.3	>50	5.1	>50	<0.1	1.1
9	0.9	48.7	1.9	>50	<0.1	3.1
10	29.2	>50	15.8	>50	1.1	>16
11	3.0	>50	3.1	>50	0.7	3.9
12	0.4	12.5	1.3	>50	0.2	1.1
13	5.3	>50	5.5	<25	2.7	>16
14	1.6	>50	28.4	>50	0.9	18.4
2	1.3	>50	3.3	>50	0.4	4.0
4	2.1	28.4	4.2	>50	0.6	2.1
3	0.8	>50	4.0	>50	1.5	6.2
15	5.9	>50	>50	>50	0.7	7.7
Iudr	5.0	6.1	1.1	0.8	ND	ND
Bvdu	5.8	5.9	2.1	0.1	ND	ND
ACV	2.4	2.8	3.9	4.4	ND	ND
AraC	0.2	0.1	0.2	0.2	ND	ND
AraT	6.6	3.6	11.6	3.6	ND	ND
AraA	10.6	18.2	26.1	27.2	ND	ND
GCVir	ND	ND	ND	ND	0.8	0.8
CDV	ND	ND	ND	ND	0.4	0.3
PFA	ND	ND	ND	ND	38	<20

5 *HSV-2 MS, HSV-1 KOS, HCMV AD169: wild type strains

*HSV-2 MS-M1, HSV-1 KOS-M1, HCMV AD169-M1: mutants selected for 4-oxo-DHQ resistance

*ND – Not Done.

Antiviral compounds identified by the present invention can conveniently be
10 administered in a pharmaceutical composition containing the compound in combination
with a suitable excipient, the composition being useful in combating viral infections.
Pharmaceutical compositions containing a compound appropriate for antiviral use are
prepared by methods and contain excipients which are well known in the art. A generally
recognized compendium of such methods and ingredients is Remington's Pharmaceutical
15 Sciences by E.W. Martin (Mark Publ. Co., 15th Ed., 1975).

Antiviral compounds identified by the present invention and their compositions can
be administered parenterally (for example, by intravenous, intraperitoneal or intramuscular

injection), topically, orally, or rectally, depending on whether the preparation is used to treat internal or external viral infections.

For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

Antiviral compounds identified by the present invention and their compositions can also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

Pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which

are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for
5 example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought
10 about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

15 Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of
20 the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable
25 carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants
30 such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers. Thickeners such as synthetic polymers, fatty acids,

fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

5 Examples of useful dermatological compositions which can be used to deliver the compounds of formula I to the skin are known to the art; for example, see Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

10 Useful dosages of the compounds of formula I can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

The compound is conveniently administered in unit dosage form; for example, containing 5 to 1000 mg, conveniently 10 to 750 mg, most conveniently, 50 to 500 mg of active ingredient per unit dosage form. The desired dose may conveniently be presented in 15 a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

20 For internal infections, the compositions can be administered orally or parenterally at dose levels, calculated as the free base, of about 0.1 to 300 mg/kg, preferably 1.0 to 30 mg/kg of mammal body weight, and can be used in man in a unit dosage form, administered one to four times daily in the amount of 1 to 1000 mg per unit dose.

For parenteral administration or for administration as drops, as for eye infections, the compounds are presented in aqueous solution in a concentration of from about 0.1 to 25 about 10%, more preferably about 0.1 to about 7%. The solution may contain other ingredients, such as emulsifiers, antioxidants or buffers.

Generally, the concentration of the compound(s) of formula I in a liquid composition, such as a lotion, will be from about 0.1-25 wt-%, preferably from about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder 30 will be about 0.1-5 wt-%, preferably about 0.5-2.5 wt-%.

The exact regimen for administration of the compounds and compositions disclosed herein will necessarily be dependent upon the needs of the individual subject being treated, the type of treatment and, of course, the judgment of the attending practitioner.

The antiviral activity of a compound of the invention can be determined using pharmacological models which are well known to the art, or using Test A described below.

The compounds of formula (I) and pharmaceutically acceptable salts thereof are useful as antiviral agents. Thus, they are useful to combat viral infections in animals, including man. The compounds are generally active against herpes viruses, and are particularly useful against the varicella zoster virus, the Epstein-Barr virus, the herpes simplex virus, the human herpes virus type 8 (HHV-8) and the cytomegalovirus (CMV).

10

CLAIMS

We claim:

1. A method of selecting compounds that inhibit herpes viruses comprising:
 - a) measuring IC_{50} of a compound of interest that inhibits a wild type herpes virus,
 - 5 b) measuring IC_{50} of the same compound that inhibits a binding domain mutant herpes virus which is the same strain as the wild type herpes virus,
 - c) comparing IC_{50} of step a with IC_{50} of step b; and
 - d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.
- 10 2. A method of selecting compounds that inhibit herpes viruses comprising:
 - a) measuring IC_{50} of a compound of interest that inhibits a binding domain mutant herpes virus,
 - b) measuring IC_{50} of the same compound that inhibits a wild type herpes virus which is
15 the same strain as the mutant herpes virus,
 - c) comparing IC_{50} of step a with IC_{50} of step b; and
 - d) selecting the compound of interest wherein the IC_{50} of step a is at least 3 times greater than the IC_{50} of step b.
- 20 3. The method of claim 1 or 2 wherein the herpes virus is HSV-1, HSV-2, HCMV, VZV, EBV, or HHV-8.
4. A method of selecting compounds that inhibit herpes viruses comprising:
 - a) measuring IC_{50} of a compound of interest that inhibits a wild type HSV-1,
 - 25 b) measuring IC_{50} of the same compound that inhibits a binding domain mutant HSV-1 which is the same strain as the wild type herpes virus,
 - c) comparing IC_{50} of step a with IC_{50} of step b; and
 - d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.
- 30 5. A method of selecting compounds that inhibit herpes viruses comprising:
 - a) measuring IC_{50} of a compound of interest that inhibits a binding domain mutant HSV-1,

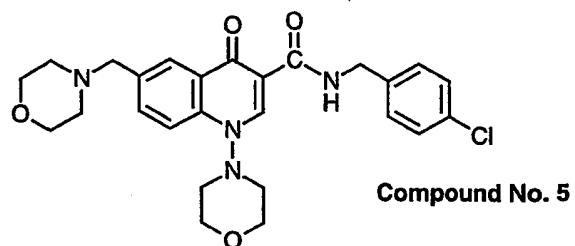
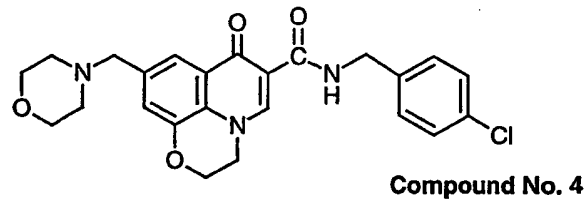
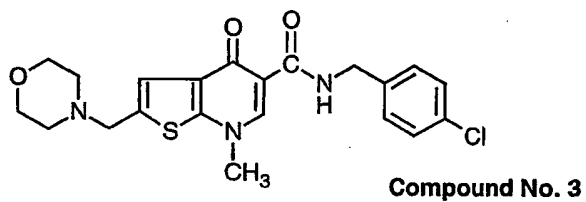
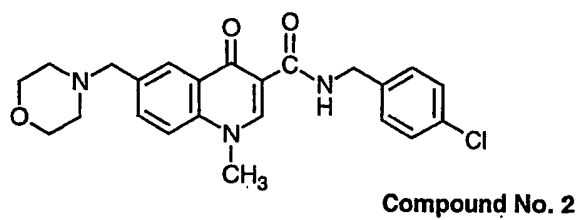
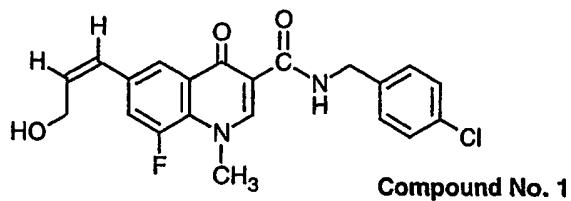
- b) measuring IC_{50} of the same compound that inhibits a wild type herpes virus which is the same strain as the mutant HSV-1,
- c) comparing IC_{50} of step a with IC_{50} of step b; and
- d) selecting the compound of interest wherein the IC_{50} of step a is at least 3 times greater than the IC_{50} of step b.
6. The method of claim 4 or 5 wherein HSV-1 is HSV-1 KOS, HSV-1 F, HSV-1 DJL or HSV-1 Patton.
7. The method of claim 5 or 6 wherein the mutation of a wild type herpes virus to mutant herpes virus is at amino acid 823 from valine to alanine.
8. A method of selecting compounds that inhibit herpes viruses comprising:
- a) measuring IC_{50} of a compound of interest that inhibits a wild type HSV-2,
- b) measuring IC_{50} of the same compound that inhibits a binding domain mutant HSV-2 which is the same strain as the wild type herpes virus,
- c) comparing IC_{50} of step a with IC_{50} of step b; and
- d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.
9. A method of selecting compounds that inhibit herpes viruses comprising:
- a) measuring IC_{50} of a compound of interest that inhibits a binding domain mutant HSV-2,
- b) measuring IC_{50} of the same compound that inhibits a wild type herpes virus which is the same strain as the mutant HSV-2,
- c) comparing IC_{50} of step a with IC_{50} of step b; and
- d) selecting the compound of interest wherein the IC_{50} of step a is at least 3 times greater than the IC_{50} of step b.
10. The method of claim 8 or 9 wherein HSV-2 is HSV-2 MS, HSV-2 35D, or HSV-2 186.
11. A method of selecting compounds that inhibit herpes viruses comprising:

- a) measuring IC_{50} of a compound of interest that inhibits a wild type HCMV,
 - b) measuring IC_{50} of the same compound that inhibits a binding domain mutant HCMV which is the same strain as the wild type herpes virus,
 - c) comparing IC_{50} of step a with IC_{50} of step b; and
 - 5 d) selecting the compound of interest wherein the IC_{50} of step b is at least 3 times greater than the IC_{50} of step a.
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12. A method of selecting compounds that inhibit herpes viruses comprising:
 - a) measuring IC_{50} of a compound of interest that inhibits a binding domain mutant HCMV,
 - 10 b) measuring IC_{50} of the same compound that inhibits a wild type herpes virus which is the same strain of the mutant HCMV,
 - c) comparing IC_{50} of step a with IC_{50} of step b; and
 - d) selecting the compound of interest wherein the IC_{50} of step a is at least 3 times
 - 15 greater than the IC_{50} of step b.
-
13. The method of claim 8 or 9 wherein HCMV is AD169.
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14. The methods of claims 1, 4, 8, or 11 wherein IC_{50} of step b is at least 5 times greater
 - 20 than the IC_{50} of step a.
-
15. The methods of claims 2, 5, 9, or 12 wherein IC_{50} of step a is at least 5 times greater than the IC_{50} of step b.
-
- 25 16. A use of compounds for manufacturing of medicinals for selectively treating diseases caused by herpes viruses in a human host comprising administering a compound to a human in need of such treatment wherein said compound inhibits herpes viruses by interaction with the binding domain in the viral DNA polymerase.
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- 30 17. A use of compounds for manufacturing of medicinals for selectively inhibiting herpes viruses in a human host comprising administering a compound to a human in need of such treatment wherein IC_{50} of the compound that inhibits a binding domain

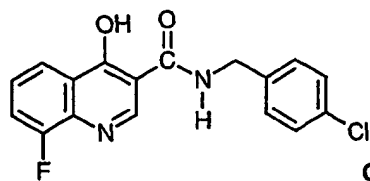
mutant herpes virus is at least 3 times greater than IC_{50} of the compound that inhibits a wild type herpes virus which is the same strain as the mutant herpes virus.

18. The use of claim 17 wherein IC_{50} of the compound that inhibits a binding domain mutant herpes virus is at least 5 times greater than IC_{50} of the compound that inhibits a wild type herpes virus which is the same strain as the mutant herpes virus.
19. The use of claim 17 wherein herpes viruses is HSV-1, HSV-2, HCMV, VZV, EBV, or HHV-8.
20. A use of compounds for manufacturing of medicinals for treating herpesviral infections in a human host wherein IC_{50} of the compound that inhibits a binding domain mutant herpes virus is at least 5 times greater than IC_{50} of the compound that inhibits a wild type herpes virus which is the same strain as the mutant herpes virus.
21. A use of compounds for manufacturing of medicinals for treating herpesviral infections in a human host wherein said compound inhibits the herpesvirus by interacting with the binding domain in the viral DNA polymerase.
22. The herpesviral infection of claim 20 or 21 which is HSV-1, HSV-2, HCMV, VZV, EBV, or HHV-8 infection.
23. A compound for the inhibiting of herpesvirus DNA polymerases wherein passage of a wild type herpes virus in the presence of said compound results a change of the wild type HSV-1 polymerases at amino acid 823 from valine to alanine.
24. A compound for inhibiting herpesvirus DNA polymerases wherein passage of a wild type herpes virus in the presence of said compound results in a change of the wild type HCMV polymerases at amino acid 823 from valine to alanine and at amino acid 824 from valine to leucine.

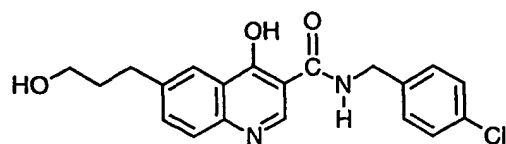
25. A mutant herpesvirus DNA molecule having a nucleotide sequence selected from a group consisting of SEQ.ID.NO. 1; SEQ.ID.NO. 3; SEQ.ID.NO. 5; SEQ.ID.NO. 7; SEQ.ID.NO. 9; and SEQ.ID.NO. 11.
- 5 26. A mutant herpesvirus polymerase amino acid molecule having an amino acid sequence selected from a group consisting of SEQ.ID.NO. 2; SEQ.ID.NO. 4; SEQ.ID.NO. 6; SEQ.ID.NO. 8; SEQ.ID.NO. 10 and SEQ.ID.NO. 12.

Figure 1 4-HQ, 4-oxo-DHQ and 4-oxo-DHTP antiviral compounds

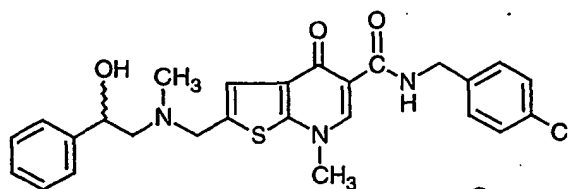
(Figure 1 continue)



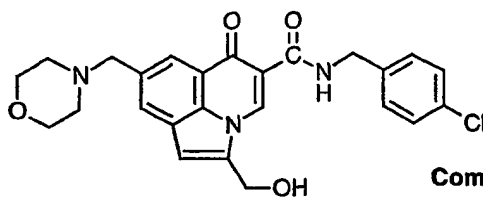
Compound No. 6



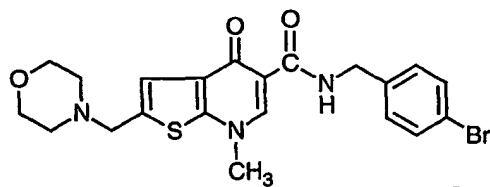
Compound No. 7



Compound No. 8

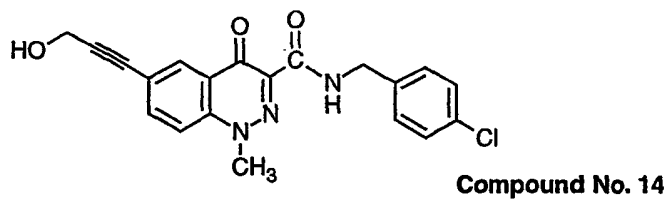
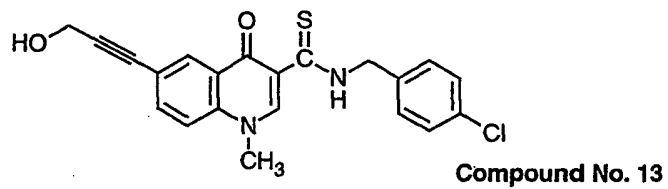
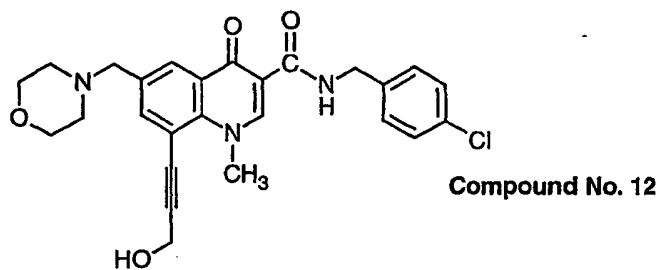
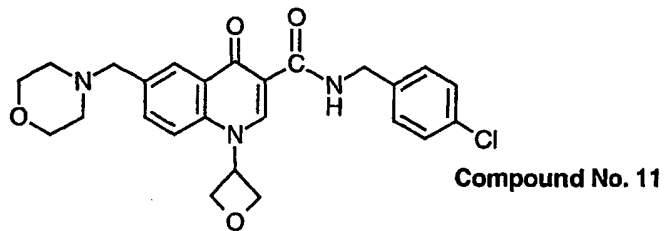


Compound No. 9

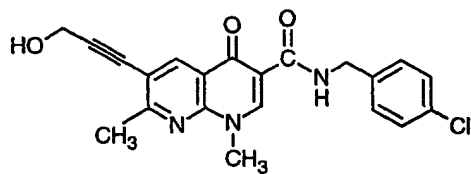


Compound No. 10

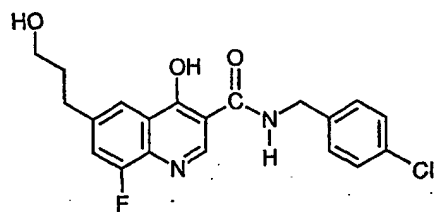
(Figure 1 continue)



(Figure 1 continue)

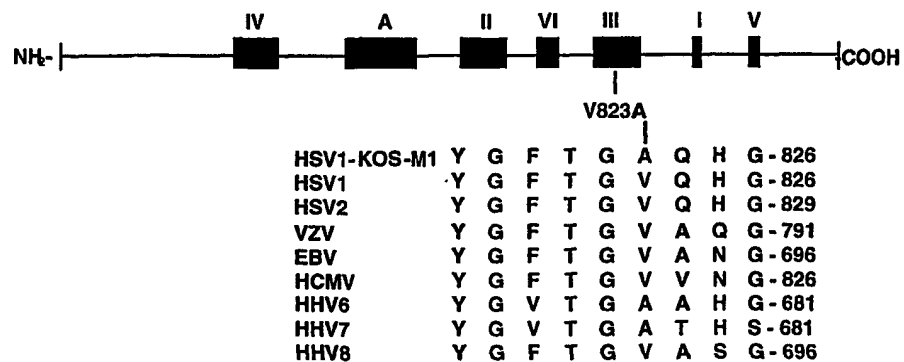


Compound No.15



Compound 17

Figure 2. The HSV1 (KOS Strain) DNA Polymerase Amino Acid 823 is Critical for Resistance to 4-Hydroxyquinolines and Related Compounds



Schematic of HSV1 polymerase illustrating the conserved regions A and I-VI found in class 2 polymerases. Also shown are the amino acid sequence for the highly conserved herpesvirus domain in region III which surrounds the HSV1 amino acid 823.

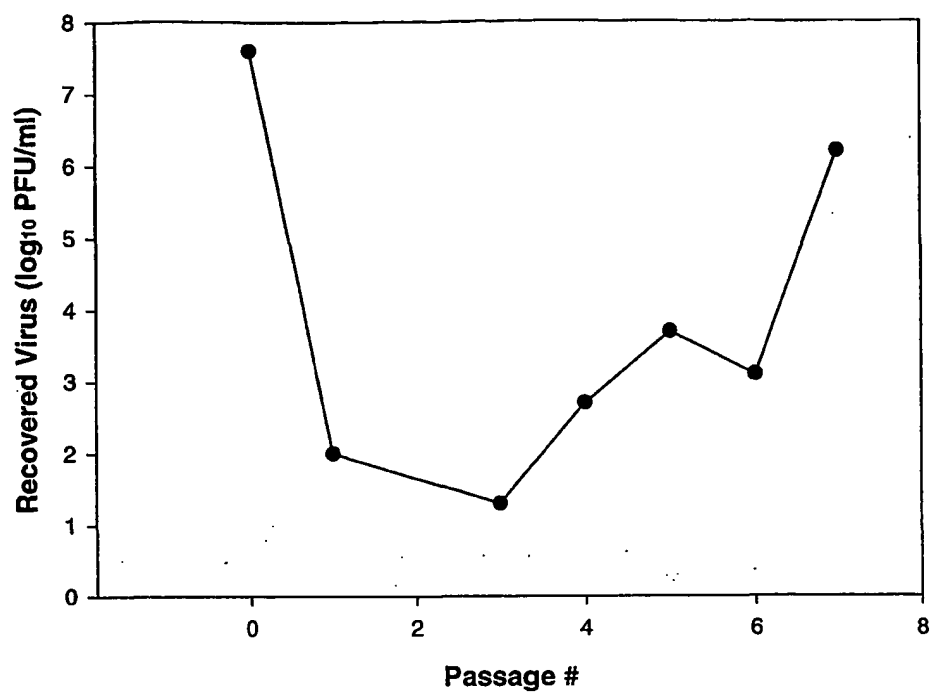
Figure 3 Serial Passage of HSV-1 in Presence of 20 μ M compound 17

Figure 4 Comparison of Wild type HSV-1 and HSV-2 DNA Polymerases Amino Acid Sequences Aligned by Amino Acid Homology*

5	HSV2-MS	MFCAAGGPTS	PGGKSAARAA	SGFFAPHNPR	GATQTAPPPC	RRQNFYNPHL	-50
	HSV2-186	MFCAAGGPAS	PGGKSAARAA	SGFFAPHNPR	GATQTAPPPC	RRQNFYNPHL	-50
	HSV1-Kos	MFSGGGGPLS	PGGKSAARAA	SGFFAPAGPR	GAGR.GPPPC	LRQNFYNPYL	-49
	HSV1-Patton	MFSGGGGPLS	PGGKSAARAA	SGFFAPAGPR	GAGR.GPPPC	LRQNFYNPYL	-49
	HSV1-DJL	MFSGGGGPLS	PGGKSAARAA	SGFFAPAGPR	GAGR.GPPPC	LRQNFYNPYL	-49
	HSV1-F	MFSGGGGPLS	PGGKSAARAA	SGFFAPAGPR	GAGR.GPPPC	LRQNFYNPYL	-49
10	HSV2-MS	AQTGTQPKAP	GPAQRHTYYS	ECDEFRFIAP	RSLDEDAPAE	QRTGVHDGRL	-100
	HSV2-186	AQTGTQPKAP	GPAQRHTYYS	ECDEFRFIAP	RSLDEDAPAE	QRTGVHDGRL	-100
	HSV1-Kos	APVGTQQKPT	GPTQRHTYYS	ECDEFRFIAP	RVLDEDAPPE	KRAGVHDGHL	-99
	HSV1-Patton	APVGTQQKPT	GPTQRHTYYS	ECDEFRFIAP	RVLDEDAPPE	KRAGVHDGHL	-99
	HSV1-DJL	APVGTQQKPT	GPTQRHTYYS	ECDEFRFIAP	RVLDEDAPPE	KRAGVHDGHL	-99
15	HSV1-F	APVGTQQKPT	GPTQRHTYYS	ECDEFRFIAP	RVLDEDAPPE	KRAGVHDGHL	-99
20	HSV2-MS	RRAPKVYCGG	DERDVLRVGP	EGFWPRRLRL	WGGADHAPKG	FDPTVTVFHV	-150
	HSV2-186	RRAPKVYCGG	DERDVLRVGP	EGFWPRRLRL	WGGADHAPEG	FDPTVTVFHV	-150
	HSV-Kos	KRAPKVYCGG	DERDVLRVGS	GGFWPRRSRL	WGGVDHAPAG	FNPTVTVFHV	-149
	HSV1-Patton	KRAPKVYCGG	DERDVLRVGS	GGFWPRRSRL	WGGVDHAPAG	FNPTVTVFHV	-149
	HSV1-DJL	KRAPKVYCGG	DERDVLRVGS	GGFWPRRSRL	WGGVDHAPAG	FNPTVTVFHV	-149
	HSV1-F	KRAPKVYCGG	DERDVLRVGS	GGFWPRRSRL	WGGVDHAPAG	FNPTVTVFHV	-149
25	HSV2-MS	YDILEHVEHA	YSMRAAQLHE	RFMDAITPAG	TVITLLGLTP	EGHRVAVHVV	-200
	HSV2-186	YDILEHVEHA	YSMRAAQLHE	RFMDAITPAG	TVITLLGLTP	EGHRVAVHVV	-200
	HSV-Kos	YDILENVEHA	YGMRAAQFHA	RFMDAITPTG	TVITLLGLTP	EGHRVAVHVV	-199
	HSV1-Patton	YDILENVEHA	YGMRAAQFHA	RFMDAITPTG	TVITLLGLTP	EGHRVAVHVV	-199
	HSV1-DJL	YDILENVEHA	YGMRAAQFHA	RFMDAITPTG	TVITLLGLTP	EGHRVAVHVV	-199
	HSV1-F	YDILENVEHA	YGMRAAQFHA	RFMDAITPTG	TVITLLGLTP	EGHRVAVHVV	-199
30	HSV2-MS	GTRQYFYMNK	AEVDRHLQCR	APRDL CERLA	AALRESPGAS	FRGISADHFE	-250
	HSV2-186	GTRQYFYMNK	AEVDRHLQCR	APRDL CERLA	AALRESPGAS	FRGISADHFE	-250
	HSV-Kos	GTRQYFYMNK	EEVDRHLQCR	APRDL CERMA	AALRESPGAS	FRGISADHFE	-249
	HSV1-Patton	GTRQYFYMNK	EEVDRHLQCR	APRDL CERMA	AALRESPGAS	FRGISADHFE	-249
	HSV1-DJL	GTRQYFYMNK	EEVDRHLQCR	APRDL CERMA	AALRESPGAS	FRGISADHFE	-249
35	HSV1-F	GTRQYFYMNK	EEVDRHLQCR	APRDL CERMA	AALRESPGAS	FRGISADHFE	-249
40	HSV2-MS	AEVVERADVY	YYETRPTLYY	RVFVRSGRAL	AYLCDNF CPA	IRKYEGGVDA	-300
	HSV2-186	AEVVERADVY	YYETRPTLYY	RVFVRSGRAL	AYLCDNF CPA	IRKYEGGVDA	-300
	HSV-Kos	AEVVERTDVY	YYETRPALFY	RVYVRSGRVL	SYLCDNF CPA	IKKYEGGVDA	-299
	HSV1-Patton	AEVVERTDVY	YYETRPALFY	RVYVRSGRVL	SYLCDNF CPA	IKKYEGGVDA	-299
	HSV1-DJL	AEVVERTDVY	YYETRPALFY	RVYVRSGRVL	SYLCDNF CPA	IKKYEGGVDA	-299
	HSV1-F	AEVVERTDVY	YYETRPALFY	RVYVRSGRVL	SYLCDNF CPA	IKKYEGGVDA	-299
45	HSV2-MS	TTRFILDNPG	FVTFGWYRLK	PGRGNAPAQ	RPPTAFGTSS	DVEFNCTADN	-350
	HSV2-186	TTRFILDNPG	FVTFGWYRLK	PGRGNAPAQ	RPPTAFGTSS	DVEFNCTADN	-350
	HSV-Kos	TTRFILDNPG	FVTFGWYRLK	PGRNNTLAQ	RAPMAFGTSS	DVEFNCTADN	-349
	HSV1-Patton	TTRFILDNPG	FVTFGWYRLK	PGRNNTLAQ	RAPMAFGTSS	DVEFNCTADN	-349
	HSV1-DJL	TTRFILDNPG	FVTFGWYRLK	PGRNNTLAQ	RAPMAFGTSS	DVEFNCTADN	-349
50	HSV1-F	TTRFILDNPG	FVTFGWYRLK	PGRNNTLAQ	RAPMAFGTSS	DVEFNCTADN	-349
55	HSV2-MS	LAVEGAMCDL	PAYKLMCFDI	ECKAGGEDEL	AFPVAERPED	LVIQISCLLY	-400
	HSV2-186	LAVEGAMCDL	PAYKLMCFDI	ECKAGGEDEL	AFPVAERPED	LVIQISCLLY	-400
	HSV-Kos	LAIEGGMSDL	PAYKLMCFDI	ECKAGGEDEL	AFPVAGHPED	LVIQISCLLY	-399
	HSV1-Patton	LAIEGGMSDL	PAYKLMCFDI	ECKAGGEDEL	AFPVAGHPED	LVIQISCLLY	-399
	HSV1-DJL	LAIEGGMSDL	PAYKLMCFDI	ECKAGGEDEL	AFPVAGHPED	LVIQISCLLY	-399
	HSV1-F	LAIEGGMSDL	PAYKLMCFDI	ECKAGGEDEL	AFPVAGHPED	LVIQISCLLY	-399
60	HSV2-MS	DLSTTALEHI	LLFSLGSCDL	PESHLSDLAS	RGLPAPVVLE	FDSEFEMLLA	-450
	HSV2-186	DLSTTALEHI	LLFSLGSCDL	PESHLSDLAS	RGLPAPVVLE	FDSEFEMLLA	-450
	HSV-Kos	DLSTTALEHV	LLFSLGSCDL	PESHLNELAA	RGLPTPVVLE	FDSEFEMLLA	-449
	HSV1-Patton	DLSTTALEHV	LLFSLGSCDL	PESHLNELAA	RGLPTPVVLE	FDSEFEMLLA	-449
	HSV1-DJL	DLSTTALEHV	LLFSLGSCDL	PESHLNELAA	RGLPTPVVLE	FDSEFEMLLA	-449
	HSV1-F	DLSTTALEHV	LLFSLGSCDL	PESHLNELAA	RGLPTPVVLE	FDSEFEMLLA	-449
65							

5	HSV2-MS	FMTFVKQYGP	EFVTGYNIIN	FDWPFVLTKL	TEIYKVPLDG	YGRMNGRGVF	-500
	HSV2-186	FMTFVKQYGP	EFVTGYNIIN	FDWPFVLTKL	TEIYKVPLDG	YGRMNGRGVF	-500
	HSV-Kos	FMTLVKQYGP	EFVTGYNIIN	FDWPFLLAKL	TDIYKVPLDG	YGRMNGRGVF	-499
	HSV1-Patton	FMTLVKQYGP	EFVTGYNIIN	FDWPFLLAKL	TDIYKVPLDG	YGRMNGRGVF	-499
	HSV1-DJL	FMTLVKQYGP	EFVTGYNIIN	FDWPFLLAKL	TDIYKVPLDG	YGRMNGRGVF	-499
	HSV1-F	FMTLVKQYGP	EFVTGYNIIN	FDWPFLLAKL	TDIYKVPLDG	YGRMNGRGVF	-499
10	HSV2-MS	RVWDIGQSHF	QKRSKIKNVNG	MVNIDMYGII	TDKVKLSSYK	LNAVAEAVLK	-550
	HSV2-186	RVWDIGQSHF	QKRSKIKNVNG	MVNIDMYGII	TDKVKLSSYK	LNAVAEAVLK	-550
	HSV-Kos	RVWDIGQSHF	QKRSKIKNVNG	MVNIDMYGII	TDKIKLSSYK	LNAVAEAVLK	-549
	HSV1-Patton	RVWDIGQSHF	QKRSKIKNVNG	MVNIDMYGII	TDKIKLSSYK	LNAVAEAVLK	-549
	HSV1-DJL	RVWDIGQSHF	QKRSKIKNVNG	MVNIDMYGII	TDKIKLSSYK	LNAVAEAVLK	-549
	HSV1-F	RVWDIGQSHF	QKRSKIKNVNG	MVNIDMYGII	TDKIKLSSYK	LNAVAEAVLK	-549
15	HSV2-MS	DKKKDLSYRD	IPAYYASGPA	QRGVIGEYCV	QDSLLVGQLF	FKFLPHLELS	-600
	HSV2-186	DKKKDLSYRD	IPAYYASGPA	QRGVIGEYCV	QDSLLVGQLF	FKFLPHLELS	-600
	HSV-Kos	DKKKDLSYRD	IPAYYAAGPA	QRGVIGEYCI	QDSLLVGQLF	FKFLPHLELS	-599
	HSV1-Patton	DKKKDLSYRD	IPAYYAAGPA	QRGVIGEYCI	QDSLLVGQLF	FKFLPHLELS	-599
	HSV1-DJL	DKKKDLSYRD	IPAYYAAGPA	QRGVIGEYCI	QDSLLVGQLF	FKFLPHLELS	-599
20	HSV1-F	DKKKDLSYRD	IPAYYAAGPA	QRGVIGEYCI	QDSLLVGQLF	FKFLPHLELS	-599
25	HSV2-MS	AVARLAGINI	TRTIYDQQOI	RVFTCLLRLA	GQKGFILPDT	QGRFRGLDKE	-650
	HSV2-186	AVARLAGINI	TRTIYDQQOI	RVFTCLLRLA	GQKGFILPDT	QGRFRGLDKE	-650
	HSV-Kos	AVARLAGINI	TRTIYDQQOI	RVFTCLLRLA	DQKGFILPDT	QGRFRGAGGE	-649
	HSV1-Patton	AVARLAGINI	TRTIYDQQOI	RVFTCLLRLA	DQKGFILPDT	QGRFRGAGGE	-649
	HSV1-DJL	AVARLAGINI	TRTIYDQQOI	RVFTCLLRLA	DQKGFILPDT	QGRFRGAGGE	-649
	HSV1-F	AVARLAGINI	TRTIYDQQOI	RVFTCLLRLA	DQKGFILPDT	QGRFRGGGGE	-649
30	HSV2-MS	APKRPAVPRG	EGERPGDGNG	DEDKDDDE..	DEDGDERE.E	VARETGGRHV	-697
	HSV2-186	APKRPAVPRG	EGERPGDGNG	DEDKDDDEEDG	DEDGDERE.E	VARETGGRHV	-697
	HSV-Kos	APKRPAVPRG	DEERP.....	EEGEDEDER	EEGGGEREPE	GARETAGRHV	-694
	HSV1-Patton	APKRPAVPRG	DEERP.....	EEGEDEDER	EEGGGEREPE	GARETAGRHV	-694
	HSV1-DJL	APKRPAVPRG	DEERP.....	EEGEDEDER	EEGGGEREPE	GARETAGRHV	-694
	HSV1-F	APKRPAVPRG	DEERP.....	EEGEDEDER	EEGGGEREPE	GARETAGRHV	-694
35	HSV2-MS	GYQGARVLDP	TSGFHVDPVV	VDFDASLYPS	IIQAHNLCFS	TLSLRPEAVA	-747
	HSV2-186	GYQGARVLDP	TSGFHVDPVV	VDFDASLYPS	IIQAHNLCFS	TLSLRPEAVA	-749
	HSV-Kos	GYQGARVLDP	TSGFHVNPVV	VDFDASLYPS	IIQAHNLCFS	TLSLRADAVA	-744
	HSV1-Patton	GYQGARVLDP	TSGFHVNPVV	VDFDASLYPS	IIQAHNLCFS	TLSLRADAVA	-744
	HSV1-DJL	GYQGARVLDP	TSGFHVNPVV	VDFDASLYPS	IIQAHNLCFS	TLSLRADAVA	-744
40	HSV1-F	GYQGARVLDP	TSGFHVNPVV	VDFDASLYPS	IIQAHNLCFS	TLSLRADAVA	-744
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	HSV2-186	HLEARDYLE	IEVGRRRLFF	VKAHVRESLL	SILLRDWLAM	RKQIRSRIPO	-799
	HSV-Kos	HLEAGDYLE	IEVGRRRLFF	VKAHVRESLL	SILLRDWLAM	RKQIRSRIPO	-794
	HSV1-Patton	HLEAGDYLE	IEVGRRRLFF	VKAHVRESLL	SILLRDWLAM	RKQIRSRIPO	-794
	HSV1-DJL	HLEAGDYLE	IEVGRRRLFF	VKAHVRESLL	SILLRDWLAM	RKQIRSRIPO	-794
	HSV1-F	HLEAGDYLE	IEVGRRRLFF	VKAHVRESLL	SILLRDWLAM	RKQIRSRIPO	-794
50	HSV2-MS	STPEEAVLLD	KQQAIAKVVC	NSVYGFTGVQ	HGLLPCLHVA	ATVTTIGREM	-847
	HSV2-186	STPEEAVLLD	KQQAIAKVVC	NSVYGFTGVQ	HGLLPCLHVA	ATVTTIGREM	-849
	HSV-Kos	SSPEEAVLLD	KQQAIAKVVC	NSVYGFTGVQ	HGLLPCLHVA	ATVTTIGREM	-844
	HSV1-Patton	SSPEEAVLLD	KQQAIAKVVC	NSVYGFTGVQ	HGLLPCLHVA	ATVTTIGREM	-844
	HSV1-DJL	SSPEEAVLLD	KQQAIAKVVC	NSVYGFTGVQ	HGLLPCLHVA	ATVTTIGREM	-844
55	HSV1-F	SSPEEAVLLD	KQQAIAKVVC	NSVYGFTGVQ	HGLLPCLHVA	ATVTTIGREM	-844
60	HSV2-MS	LLATRAYVHA	RWAEFDQLLA	DFPEAAGMRA	PGPYSMRIY	GDTDSIFVLC	-897
	HSV2-186	LLATRAYVHA	RWAEFDQLLA	DFPEAAGMRA	PGPYSMRIY	GDTDSIFVLC	-899
	HSV-Kos	LLATREYVHA	RWAAFEQLLA	DFPEAADMRA	PGPYSMRIY	GDTDSIFVLC	-894
	HSV1-Patton	LLATREYVHA	RWAAFEQLLA	DFPEAADMRA	PGPYSMRIY	GDTDSIFVLC	-894
	HSV1-DJL	LLATREYVHA	RWAAFEQLLA	DFPEAADMRA	PGPYSMRIY	GDTDSIFVLC	-894
	HSV1-F	LLATREYVHA	RWAAFEQLLA	DFPEAADMRA	PGPYSMRIY	GDTDSIFVLC	-894
65	HSV2-MS	RGLTAAGLVA	MGDKMASHIS	RALFLPPIKL	ECEKTFTKLL	LIAKKKYIGV	-947
	HSV2-186	RGLTAAGLVA	MGDKMASHIS	RALFLPPIKL	ECEKTFTKLL	LIAKKKYIGV	-949
	HSV-Kos	RGLTAAGLTA	MGDKMASHIS	RALFLPPIKL	ECEKTFTKLL	LIAKKKYIGV	-944
	HSV1-Patton	RGLTAAGLTA	MGDKMASHIS	RALFLPPIKL	ECEKTFTKLL	LIAKKKYIGV	-944

	HSV1-DJL	RGLTAAGLTA	VGDKMASHIS	RALFLPPIKL	ECEKTFTKLL	LIAKKKYIGV	-944
	HSV1-F	RGLTAAGLTA	VGDKMASHIS	RALFLSPIKL	ECEKTFTKLL	LIAKKKYIGV	-944
5	HSV2-MS	ICGGKMLIKG	VDLVRKNNCA	FINRTSRALV	DLLFYDDTVS	GAAAAAERP	-997
	HSV2-186	ICGGKMLIKG	VDLVRKNNCA	FINRTSRALV	DLLFYDDTVS	GAAAAAERP	-999
	HSV-Kos	IYGGKMLIKG	VDLVRKNNCA	FINRTSRALV	DLLFYDDTVS	GAAAAAERP	-994
	HSV1-Patton	IYGGKMLIKG	VDLVRKNNCA	FINRTSRALV	DLLFYDDTVS	GAAAAAERP	-994
	HSV1-DJL	IYGGKMLIKG	VDLVRKNNCA	FINRTSRALV	DLLFYDDTVS	GAAAAAERP	-994
	HSV1-F	IYGGKMLIKG	VDLVRKNNCA	FINRTSRALV	DLLFYDDTVS	GAAAAAERP	-994
10	HSV2-MS	AEWLARPLP	EGLQAFGAVL	VDAHRRITDP	ERDIQDFVLT	AELSRHPRAY	-1047
	HSV2-186	AEWLARPLP	EGLQAFGAVL	VDAHRRITDP	ERDIQDFVLT	AELSRHPRAY	-1049
	HSV-Kos	AEWLARPLP	EGLQAFGAVL	VDAHRRITDP	ERDIQDFVLT	AELSRHPRAY	-1044
	HSV1-Patton	AEWLARPLP	EGLQAFGAVL	VDAHRRITDP	ERDIQDFVLT	AELSRHPRAY	-1044
15	HSV1-DJL	AEWLARPLP	EGLQAFGAVL	VDAHRRITDP	ERDIQDFVLT	AELSRHPRAY	-1044
	HSV1-F	AEWLARPLP	EGLQAFGAVL	VDAHRRITDP	ERDIQDFVLT	AELSRHPRAY	-1044
20	HSV2-MS	TNKRLAHLTV	YYKLMARRAQ	VPSIKDRIPY	VIVAQTREVE	ETVARLAALR	-1097
	HSV2-186	TNKRLAHLTV	YYKLMARRAQ	VPSIKDRIPY	VIVAQTREVE	ETVARLAALR	-1099
	HSV-Kos	TNKRLAHLTV	YYKLMARRAQ	VPSIKDRIPY	VIVAQTREVE	ETVARLAALR	-1094
	HSV1-Patton	TNKRLAHLTV	YYKLMARRAQ	VPSIKDRIPY	VIVAQTREVE	ETVARLAALR	-1094
	HSV1-DJL	TNKRLAHLTV	YYKLMARRAQ	VPSIKDRIPY	VIVAQTREVE	ETVARLAALR	-1094
	HSV1-F	TNKRLAHLTV	YYKLMARRAQ	VPSIKDRIPY	VIVAQTREVE	ETVARLAALR	-1094
25	HSV2-MS	ELDAAAPGDE	PAPPAALPSP	AKRPRETPSH	ADPPGGASKP	RKLLVSELAE	-1147
	HSV2-186	ELDAAAPGDE	PAPPAALPSP	AKRPRETPSH	ADPPGGASKP	RKLLVSELAE	-1149
	HSV-Kos	ELDAAAPGDE	PAPPAALPSP	AKRPRETPSH	ADPPGGASKP	RKLLVSELAE	-1144
	HSV1-Patton	ELDAAAPGDE	PAPPAALPSP	AKRPRETPSP	ADPPGGASKP	RKLLVSELAE	-1144
	HSV1-DJL	ELDAAAPGDE	PAPPAALPSP	AKRPRETPSP	ADPPGGASKP	RKLLVSELAE	-1144
30	HSV1-F	ELDAAAPGDE	PAPPAALPSP	AKRPRETPLH	ADPPGGASKP	RKLLVSELAE	-1144
35	HSV2-MS	DPGYAIARGV	PLNTDYYFSH	LLGAACVTFK	ALFGNNAKIT	ESLLKRFIPE	-1197
	HSV2-186	DPGYAIARGV	PLNTDYYFSH	LLGAACVTFK	ALFGNNAKIT	ESLLKRFIPE	-1199
	HSV-Kos	DPYAIAGHV	ALNTDYYFSH	LLGAACVTFK	ALFGNNAKIT	ESLLKRFIPE	-1194
	HSV1-Patton	DPYAIAGHV	ALNTDYYFSH	LLGAACVTFK	ALFGNNAKIT	ESLLKRFIPE	-1194
	HSV1-DJL	DPYAIAGHV	ALNTDYYFSH	LLGAACVTFK	ALFGNNAKIT	ESLLKRFIPE	-1194
	HSV1-F	DPYAIAGHV	ALNTDYYFSH	LLGAACVTFK	ALFGNNAKIT	ESLLKRFIPE	-1194
40	HSV2-MS	TWHPPDDVAA	RLRAAGFGPA	GAGATAEETR	RMLHRAFDTL	A*	-1238
	HSV2-186	TWHPPDDVAA	RLRAAGFGPA	GAGATAEETR	RMLHRAFDTL	A*	-1240
	HSV-Kos	VWHPPDDVAA	RLRAAGFGAV	GAGATAEETR	RMLHRAFDTL	A*	-1235
	HSV1-Patton	VWHPPDDVTA	RLRAAGFGAV	GAGATAEETR	RMLHRAFDTL	A*	-1235
	HSV1-DJL	VWHPPDDVAA	RLRTAGFGAV	GAGATAEETR	RMLHRAFDTL	A*	-1235
	HSV1-F	VWHPPDDVAA	RLRAAGFGAV	GAGATAEETR	RMLHRAFDTL	A*	-1235
45							

*Amino acid alignment demonstrates difference in amino acid's sequences.

*The gaps "....." indicate missing amino acids relative to other stanins.

*Wild HSV2-MS is listed as SEQ. ID NO 14.

*Wild HSV2-186 is listed as SEQ. ID NO 15.

50 *Wild HSV-Kos is listed as SEQ. ID NO 16.

*Wild HSV1-Patton is listed as SEQ. ID NO 17.

*Wild HSV1-DJL is listed as SEQ. ID NO 18.

*Wild HSV1-F is listed as SEQ. ID NO 19.

55

Figure 5 DNA and amino acid sequence list**SEQ. ID. NO. 1 DNA sequence of DNA polymerase gene for HSV2-MS-M1**

5 1 ATGTTTTGTG CCGCGGGCGG CCCGACTTCC CCCGGGGGGA AGTCGGCGGC
 51 TCGGGCGGCG TCTGGGTTTT TTGCCCCCA CAACCCCGG GGAGCCACCC
 101 AGACGGCACC GCCGCCTTGC CGCCGGCAGA ACTTCTACAA CCCCCACCTC
 10 151 GCTCAGACCG GAACGCAGCC AAAGGCCCCC GGGCCGGCTC AGCGCCATAC
 201 GTACTACAGC GAGTGCGACG AATTTCGATT TATCGCCCCG CGTTCGCTGG
 251 ACGAGGACGC CCCC GCGGAG CAGCGCACCG GGGTCCACGA CGGCCGCCTC
 301 CGGCGCGCCC CTAAGGTGTA CTGCGGGGGG GACGAGCGCG ACGTCCTCCG
 351 CGTGGGCCCC GAGGGCTTCT GGCCGCGTCG CTTGCGCCTG TGGGGCGGTG
 20 401 CGGACCATGC CCCCAAGGGG TTCGACCCA CCGTCACCGT CTTCCACGTG
 451 TACGACATCC TGGAGCACGT GGAACACGCG TACAGCATGC GCGCCGCCCA
 501 GCTCCACGAG CGATTATGG ACGCCATCAC GCCCGCCGGG ACCGTCATCA
 25 551 CGCTTCTGGG TCTGACCCCC GAAGGCCATC GCGTCGCCGT TCACGTCTAC
 601 GGCACGCGGC AGTACTTTTA CATGAACAAG GCGGAGGTGG ATCGGCACCT
 30 651 GCAGTGCCGT GCCCCGCGCG ATCTCTGCGA GCGCCTGGCG GCGGCCCTGC
 701 GCGAGTCGCC GGGGGCGTCG TTCCGCGGCA TCTCCGCGGA CCACTTCGAG
 751 GCGGAGGTGG TGGAGCGCGC CGACGTGTAC TATTACGAAA CGCGCCCGAC
 801 CCTGTACTAC CGCGTCTTCG TGCGAAGCGG GCGCGCGCTG GCCTACCTGT
 851 GCGACAACTT TTGCCCCGCG ATCAGGAAGT ACGAGGGGGG CGTCGACGCC
 40 901 ACCACCCGGT TTATCCTGGA CAACCCGGGG TTTGTACCT TCGGCTGGTA
 951 CCGCCTCAAG CCCGGCCGCG GGAACGCGCC GGCCCAACCG CGCCCCCGA
 1001 CGGCGTTCGG AACCTCGAGC GACGTCGAGT TTAAGTGCAC GGCGGACAAC
 1051 CTGGCCGTCG AGGGGGCCAT GTGTGACCTG CCGGCCTACA AGCTCATGTG
 1101 CTTGATATC GAATGCAAGG CCGGGGGGGA GGACGAGCTG GCCTTTCGG
 50 1151 TCGCGGAACG CCCGGAAGAC CTCGTCATCC AGATCTCCTG TCTGCTCTAC
 1201 GACCTGTCCA CCACCGCCCT CGAGCACATC CTCCTGTTTT CGCTCGGATC
 1251 CTGCGACCTC CCCGAGTCCC ACCTCAGCGA TCTCGCCTCC AGGGGCCTGC
 55 1301 CGGCCCCCGT CGTCCTGGAG TTTGACAGCG AATTCGAGAT GCTGCTGGCC

1351 TTCATGACCT TCGTCAAGCA GTACGGCCCC GAGTTCGTGA CCGGGTACAA
1401 CATCATCAAC TTCGACTGGC CCTTCGTCCT GACCAAGCTG ACGGAGATCT
5 1451 ACAAGGTCCC GCTCGACGGG TACGGGCGCA TGAACGGCCG GGGTGTGTTC
1501 CGCGTGTGGG ACATCGGCCA GAGCCACTTT CAGAAGCGCA GCAAGATCAA
1551 GGTGAACGGG ATGGTGAACA TCGACATGTA CGGCATCATC ACCGACAAGG
10 1601 TCAAACCTCTC CAGCTACAAG CTGAACGCCG TCGCCGAGGC CGTCTTGAAG
1651 GACAAGAAGA AGGATCTGAG CTACCGCGAC ATCCCCGCCT ACTACGCCTC
15 1701 CGGGCCCCGCG CAGCGCGGGG TGATCGGCCA GTATTGTGTG CAGGACTCGC
1751 TGCTGGTCGG GCAGCTGTTT TTCAAGTTTC TGCCGCACCT GGAGCTTTCC
1801 GCCGTCGCGC GCCTGGCGGG CATCAACATC ACCCGCACCA TCTACGACGG
20 1851 CCAGCAGATC CGCGTCTTCA CGTGCCTCCT GCGCCTTGCG GGCCAGAAGG
1901 GCTTCATCCT GCCGGACACC CAGGGGCGGT TTCGGGGCCT CGACAAGGAG
25 1951 GCGCCCAAGC GCCCGGCCGT GCCTCGGGGG GAAGGGGAGC GGCCGGGGGA
2001 CGGGAACGGG GACGAGGATA AGGACGACGA CGAGGACGAG GACGGGGACG
2051 AGCGCGAGGA GGTCGCGCGC GAGACCGGGG GCCGGCACGT TGGGTACCAG
30 2101 GGGGCCCCGG TCCTCGACCC CACCTCCGGG TTTCACGTCG ACCCCGTGGT
2151 GGTGTTTGAC TTGCCAGCC TGTACCCAG CATCATCCAG GCCCACAACC
35 2201 TGTGCTTCAG TACGCTCTCC CTGCGGGCCG AGGCCGTCGC GCACCTGGAG
2251 GCGGACCGGG ACTACCTGGA GATCGAGGTG GGGGGCCGAC GGCTGTTCTT
2301 CGTGAAGGCC CACGTACGCG AGAGCCTGCT GAGCATCCTG CTGCGCGACT
40 2351 GGCTGGCCAT GCGAAAGCAG ATCCGCTCGC GGATCCCCCA GAGCACCCCC
2401 GAGGAGGCCG TCCTCCTCGA CAAGCAACAG GCCGCCATCA AGGTGGTGTG
45 2451 CAACTCGGTG TACGGGTTC CCGGGGCGCA GCACGGTCTT CTGCCCTGCC
2501 TGCACGTGGC CGCCACCGTG ACGACCATCG GCCGCGAGAT GCTCCTCGCG
2551 ACGCGCGCGT ACGTGCACGC GCGCTGGGCG GAGTTCGATC AGCTGCTGGC
50 2601 CGACTTTCCG GAGGCGGCCG GCATGCGCGC CCCCAGTCCG TACTCCATGC
2651 GCATCATCTA CGGGGACACG GACTCCATTT TCGTTTTGTG CCGCGGCCTC
55 2701 ACGGCCGCGG GCCTGGTGGC CATGGGCGAC AAGATGGCGA GCCACATCTC
2751 GCGCGCGCTG TTCCTCCCCC CGATCAAGCT CGAGTGCGAA AAAACGTTCA
2801 CCAAGCTGCT GCTCATCGCC AAGAAAAAGT ACATCGGCGT CATCTGCGGG
60

2851 GGCAAGATGC TCATCAAGGG CGTGGATCTG GTGCGCAAAA ACAACTGCGC
2901 GTTTATCAAC CGCACCTCCA GGGCCCTGGT CGACCTGCTG TTTTACGACG
5 2951 ATACCGTATC CGGAGCGGCC GCCGCGTTAG CCGAGCGCCC CGCAGAGGAG
3001 TGGCTGGCGC GACCCCTGCC CGAGGGACTG CAGGCGTTCG GGGCCGTCCT
3051 CGTAGACGCC CATCGGCGCA TCACCGACCC GGAGAGGGAC ATCCAGGACT
10 3101 TTGTCTCAC CGCCGAACTG AGCAGACACC CGCGCGCGTA CACCAACAAG
3151 CGCCTGGCCC ACCTGACGGT GTATTACAAG CTCATGGCCC GCCGCGCGCA
15 3201 GGTCCCGTCC ATCAAGGACC GGATCCCGTA CGTGATCGTG GCCCAGACCC
3251 GCGAGGTAGA GGAGACGGTC GCGCGGCTGG CCGCCCTCCG CGAGCTAGAC
3301 GCCGCCGCC CAGGGGACGA GCCCGCCCCC CCAGCGGCCC TGCCCTCCCC
20 3351 GGCCAAGCGC CCCCAGGAGA CGCCGTCGCA TGCCGACCCC CCGGGAGGCG
3401 CGTCCAAGCC CCGCAAGCTG CTGGTGTCCG AGCTGGCGGA GGATCCCGGG
25 3451 TACGCCATCG CCCGGGGCGT TCCGCTCAAC ACGGACTATT ACTTCTCGCA
3501 CCTGCTGGGG GCGGCCTGCG TGACGTTCAA GGCCCTGTTT GGAAATAACG
3551 CCAAGATCAC CGAGAGTCTG TTAAAGAGGT TTATTCCCGA GACGTGGCAC
30 3601 CCCCCGACG ACGTGGCCGC GCGGCTCAGG GCCGCGGGGT TCGGGCCGGC
3651 GGGGGCCGGC GCTACGGCGG AGGAAACTCG TCGAATGTTG CATAGAGCCT
35 3701 TTGATACTCT AGCATGA

SEQ. ID. NO. 2 Amino acid sequence of DNA polymerase for HSV2-MS-M1

1 MFCAAGGPTS PGGKSAARAA SGFFAPHNPR GATQTAPPPC RRQNFYNPHL
5 51 AQTGTQPKAP GPAQRHTYYS ECDEFRLFAP RSLDEDAPAE QRTGVHDGRL
101 RRAPKVYCGG DERDVLRVGP EGFWRRLRL WGGADHAPKG FDPTVTVFHV
151 YDILEHVEHA YSMRAAQLHE RFMDAITPAG TVITLLGLTP EGHRVAVHVY
10 201 GTRQYFYMNK AEVDRHLQCR APRDLCERLA AALRESPGAS FRGISADHFE
251 AEVVERADV Y YETRPTLYY RVFVRSGRAL AYLCDNFCPA IRKYEGGVDA
15 301 TTRFILDNPG FVTFGWYRLK PGRGNAPAQP RPPTAFGTSS DVEFNCTADN
351 LAVEGAMCDL PAYKLMCFDI ECKAGGEDEL AFPVAERPED LVIQISCLLY
401 DLSTTALEHI LLFSLGSCDL PESHLSDLAS RGLPAPVVLE FDSEFEMLLA
20 451 FMTFVKQYGP EFVTGYNIIN FDWPFVLTCL TEIYKVPLDG YGRMNNGRGVF
501 RVWDIGQSHF QKRSKIKVNG MVNIDMYGII TDKVKLSSYK LNAVAEAVLK
25 551 DKKKDLSYRD IPAYYASGPA QRGVIGEYCV QDSLLVGQLF FKFLPHLELS
601 AVARLAGINI TRTIYDGQOI RVFTCLLRLA GQKGFILPDT QGRFRGLDKE
651 APKRPAVPRG EGERPGDGNG DEDKDDDEDE DGDREEVAR ETGGRHVGYQ
30 701 GARVLDPTSG FHVDPVVVFD FASLYPSIIQ AHNLCFSTLS LRPEAVAHLE
751 ADRDYLEIEV GGRRLFFVKA HVRESLLSIL LRDWLAMRKQ IRSRIPQSTP
35 801 EEAVLLDKQQ AAIKVV CNSV YGFTGAQHGL LPCLHVAATV TTIGREMLLA
851 TRAYVHARWA EFDQLLADFP EAAGMRAPGP YSMRIY GDT DSIFVLCRGL
901 TAAGLVAMGD KMASHISRAL FLPPIKLECE KTFTKLLLIA KKKYIGVICG
40 951 GKMLIKGVDL VRKNNCAFIN RTSRALVDLL FYDDTVSGAA AALAERP AEE
1001 WLARPLPEGL QAFGAVLVDA HRRITDPERD IQDFVLTAEL SRHPRAYTNK
45 1051 RLAHLTVYYK LMARRAQVPS IKDRIPYVIV AQTREVEETV ARLAALRELD
1101 AAAPGDEPAP PAALPSPAKR PRETPSHADP PGGASKPRKL LVSELAEDPG
1151 YAIARGVPLN TDYYFSHLLG AACVTFKALF GNNAKITESL LKRFPETWH
50 1201 PPDDVAARLR AAGFGPAGAG ATAEETRRML HRAFDTLA*

SEQ.ID.NO. 3 DNA sequence of DNA polymerase gene for HSV2-186-M1

1 ATGTTTTGTG CCGCGGGCGG CCCGGCTTCC CCCGGGGGGA AGTCGGCGGC
5 51 TCGGGCGGCG TCTGGGTTTT TTGCCCCCA CAACCCCGG GGAGCCACCC
101 AGACGGCACC GCCGCCTTGC CGCCGGCAGA ACTTCTACAA CCCCACCTC
151 GCTCAGACCG GAACGCAGCC AAAGGCCCCC GGGCCGGCTC AGCGCCATAC
10 201 GTACTACAGC GAGTGCGACG AATTTGATT TATCGCCCCG CGTTCGCTGG
251 ACGAGGACGC CCCCGCGGAG CAGCGCACC GGTTCACGA CGGCCGCCTC
15 301 CGGCGCGCCC CTAAGGTGTA CTGCGGGGGG GACGAGCGCG ACGTCCTCCG
351 CGTGGGCCCC GAGGGCTTCT GGCCGCGTCG CTTGCGCCTG TGGGGCGGTG
401 CGGACCATGC CCCCAGGGG TTCGACCCA CCGTCACCGT CTTCCACGTG
20 451 TACGACATCC TGGAGCACGT GGAACACGCG TACAGCATGC GCGCCGCCCA
501 GCTCCACGAG CGATTTATGG ACGCCATCAC GCCC GCCGG ACCGTCATCA
25 551 CGCTTCTGGG TCTGACCCCC GAAGGCCATC GCGTCGCCGT TCACGTCTAC
601 GGCACGCGGC AGTACTTTTA CATGAACAAG GCGGAGGTGG ATCGGCACCT
651 GCAGTGCCGT GCCCCGCGCG ATCTCTGCGA GCGCCTGGCG GCGGCCCTGC
30 701 GCGAGTCGCC GGGGGCGTCG TTCCGCGGCA TCTCCGCGGA CCACTTCGAG
751 GCGGAGGTGG TGGAGCGCGC CGACGTGTAC TATTACGAAA CGCGCCCGAC
35 801 CCTGTACTAC CGCGTCTTCG TCGAAGCGG GCGCGCGCTG GCCTACCTGT
851 GCGACAACTT TTGCCCCGCG ATCAGGAAGT ACGAGGGGGG CGTCGACGCC
901 ACCACCCGGT TTATCCTGGA CAACCCGGGG TTTGTACCT TCGGCTGGTA
40 951 CCGCCTCAAG CCCGGCCGCG GGAACGCGCC GGCCCAACCG CGCCCCCGA
1001 CGGCGTTCGG AACCTCGAGC GACGTCGAGT TTAAGTGCAC GGCGGACAAC
45 1051 CTGGCCGTCG AGGGGGCCAT GTGTGACCTG CCGGCCTACA AGCTCATGTG
1101 CTTGATATC GAATGCAAGG CCGGGGGGGA GGACGAGCTG GCCTTTCCGG
1151 TCGCGGAACG CCCGGAAGAC CTCGTCATCC AGATCTCCTG TCTGCTCTAC
50 1201 GACCTGTCCA CCACCGCCCT CGAGCACATC CTCCTGTTTT CGCTCGGATC
1251 CTGCGACCTC CCCGAGTCCC ACCTCAGCGA TCTCGCCTCC AGGGGCCTGC
55 1301 CGGCCCCCGT CGTCCTGGAG TTTGACAGCG AATTCGAGAT GCTGCTGGCC
1351 TTCATGACCT TCGTCAAGCA GTACGGCCCC GAGTTCGTGA CCGGGTACAA
1401 CATCATCAAC TTCGACTGGC CCTTCGTCCT GACCAAGCTG ACGGAGATCT
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1451 ACAAGGTCCC GCTCGACGGG TACGGGCGCA TGAACGGCCG GGGTGTGTTC
1501 CGCGTGTGGG ACATCGGCCA GAGCCACTTT CAGAAGCGCA GCAAGATCAA
5 1551 GGTGAACGGG ATGGTGAACA TCGACATGTA CGGCATCATC ACCGACAAGG
1601 TCAAACCTCTC CAGCTACAAG CTGAACGCCG TCGCCGAGGC CGTCTTGAAG
1651 GACAAGAAGA AGGATCTGAG CTACCGCGAC ATCCCCGCCT ACTACGCCTC
10 1701 CGGGCCCCGCG CAGCGCGGGG TGATCGGCGA GTATTGTGTG CAGGACTCGC
1751 TGCTGGTCGG GCAGCTGTTC TTCAAGTTTC TGCCGCACCT GGAGCTTTCC
1801 GCCGTCGCGC GCCTGGCGGG CATCAACATC ACCCGCACCA TCTACGACGG
1851 CCAGCAGATC CGCGTCTTCA CGTGCCTCCT GCGCCTTGCG GGCCAGAAGG
1901 GCTTCATCCT GCCGGACACC CAGGGGCGGT TTCGGGGCCT CGACAAGGAG
20 1951 GCGCCCAAGC GCGCGGCCGT GCCTCGGGGG GAAGGGGAGC GGCCGGGGGA
2001 CGGGAACGGG GACGAGGATA AGGACGACGA CGAGGACGGG GACGAGGACG
25 2051 GGGACGAGCG CGAGGAGGTC GCGCGCGAGA CCGGGGGCCG GCACGTTGGG
2101 TACCAGGGGG CCCGGGTCCT CGACCCACCC TCCGGGTTTC ACGTCGACCC
2151 CGTGGTGGTG TTTGACTTTG CCAGCCTGTA CCCCAGCATC ATCCAGGCCC
30 2201 ACAACCTGTG CTTAGTACG CTCTCCCTGC GGCCGAGGC CGTCGCGCAC
2251 CTGGAGGCGG ACCGGGACTA CCTGGAGATC GAGGTGGGGG GCCGACGGCT
35 2301 GTTCTTCGTG AAGGCCACG TACGCGAGAG CCTGCTGAGC ATCCTGCTGC
2351 GCGACTGGCT GGCCATGCGA AAGCAGATCC GCTCGCGGAT CCCCAGAGC
2401 CCCCCGAGG AGGCCGTCCT CCTCGACAAG CAACAGGCCG CCATCAAGGT
40 2451 GGTGTGCAAC TCGGTGTACG GGTTACCGG GCGCAGCAC GGTCTTCTGC
2501 CCTGCCTGCA CGTGGCCGCC ACCGTGACGA CCATCGGCCG CGAGATGCTC
45 2551 CTCGCGACGC GCGCGTACGT GCACGCGCGC TGGGCGGAGT TCGATCAGCT
2601 GCTGGCCGAC TTTCCGAGG CGGCCGGCAT GCGCGCCCCC GTTCCGTACT
2651 CCATGCGCAT CATCTACGGG GACACGGA CTATTTTCGT TTTGTGCCGC
50 2701 GGCCTCACGG CCGCGGGCCT GGTGGCCATG GGCGACAAGA TGGCGAGCCA
2751 CATCTCGCGC GCGCTGTTCC TCCCCCGAT CAAGCTCGAG TGCGAAAAA
55 2801 CGTTCACCAA GCTGCTGCTC ATCGCCAAGA AAAAGTACAT CGGCGTCATC
2851 TGCGGGGGCA AGATGCTCAT CAAGGGCGTG GATCTGGTGC GCAAAAACAA
2901 CTGCGCGTTT ATCAACCGCA CCTCCAGGGC CCTGGTCGAC CTGCTGTTTT
60

2951 ACGACGATAC CGTATCCGGA GCGGCCGCGG CGTTAGCCGA GCGCCCCGCA
3001 GAGGAGTGGC TGGCGCGACC CCTGCCCGAG GGA CTGCAGG CGTTCGGGGC
5 3051 CGTCCTCGTA GACGCCCATC GGC GCATCAC CGACCCGGAG AGGGACATCC
3101 AGGACTTTGT CCTCACCGCC GAACTGAGCA GACACCCGCG CGCGTACACC
3151 AACAAGCGCC TGGCCCACCT GACGGTGTAT TACAAGCTCA TGGCCCCGCCG
10 3201 CGCGCAGGTC CCGTCCATCA AGGACCGGAT CCCGTACGTG ATCGTGGCCC
3251 AGACCCGCGA GG TAGAGGAG ACGGTCGCGC GGCTGGCCGC CCTCCGCGAG
15 3301 CTAGACGCCG CCGCCCCAGG GGACGAGCCC GCCCCCCCAG CGGCCCTGCC
3351 CTCCCCGGCC AAGCGCCCCC GGGAGACGCC GTCGCATGCC GACCCCCCGG
3401 GAGGCGCGTC CAAGCCCCGC AAGCTGCTGG TGTCCGAGCT GGC GGAGGAT
20 3451 CCCGGGTACG CCATCGCCCC GGGCGTTCCG CTCAACACGG ACTATTACTT
3501 CTCGCACCTG CTGGGGGCGG CCTGCGTGAC GTTCAAGGCC CTGTTTGGAA
25 3551 ATAACGCCAA GATCACCAG AGTCTGTTAA AGAGGTTTAT TCCCGAGACG
3601 TGGCACCCCC CGGACGACGT GGCCGCGCGG CTCAGGGCCG CGGGGTTCGG
3651 GCCGGCGGGG GCCGGCGCTA CGGCGGAGGA AACTCGTCGA ATGTTGCATA
30 3701 GAGCCTTTGA TACTCTAGCA TGA

SEQ.ID.NO. 4 Amino acid sequence of DNA polymerase for HSV2-186-M1

5 1 MFCAAGGPAS PGGKSAARAA SGFFAPHNPR GATQTAPPPC RRQNFYNPHL
 51 AQTGTQPKAP GPAQRHTYYS ECDEFRFIAP RSLDEDAPAE QRTGVHDGRL
 101 RRAPKVYCGG DERDVLRVGP EGFWRRLRL WGGADHAPEG FDPTVTVFHV
 10 151 YDILEHVEHA YSMRAAQLHE RFMDAITPAG TVITLLGLTP EGHRAVAVHV
 201 GTRQYFYMNK AEVDRHLQCR APRDLCERLA AALRESPGAS FRGISADHFE
 15 251 AEVVERADVY YYETRPTLYY RVFVRSGRAL AYLCDNF CPA IRKYEGGVDA
 301 TTRFILDNPG FVTFGWYRLK PGRGNAPAQP RPPTAFGTSS DVEFNCTADN
 351 LAVEGAMCDL PAYKLMCFDI ECKAGGEDEL AFPVAERPED LVIQISCLLY
 20 401 DLSTTALEHI LLFSLGSCDL PESHLSDLAS RGLPAPVVLE FDSEFEMLLA
 451 FMTFVKQYGP EFVTGYNIIN FDWPFVLT KL TEIYKVPLDG YGRMN GRGVF
 25 501 RVWDIGQSHF QKRSEKIVNG MVNIDMYGII TDKVKLSSYK LNAVAEAVLK
 551 DKKKDLSEYD IPAYYASGPA QRGVIGEYCV QDSLLVGQLF FKFLPHLELS
 601 AVARLAGINI TRTTYDGQOI RVFTCLLRLA GQKGFILPDT QGRFRGLDKE
 30 651 APKRPAVPRG EGERPGDGNG DEDKDDDEDG DEDGDERE EV ARETGGRHVG
 701 YQGARVLDPT SGFHVDPVVV FDFASLYPSI IQAHNLCFST LSLRPEAVAH
 35 751 LEADRDYLEI EVGGRRLFFV KAHVRESLLS ILLRDWLAMR KQIRSRIPQS
 801 PPEEAVLLDK QQAAIKVVCN SVYGFTGAQH GLLPCLHVAA TVTTIGREML
 851 LATRAYVHAR WAEFDQLLAD FPEAAGMRAP GPYSMRIY G DTDSIFVLCR
 40 901 GLTAAGLVAM GDKMASHISR ALFLPPIKLE CEKTFTKLLL IAKKKYIGVI
 951 CGGKMLIKGV DLVRKNNCAF INRTSRALVD LLFYDDTVSG AAAALAERPA
 45 1001 EEWLARPLPE GLQAFGAVLV DAHRRITDPE RDIQDFVLT A ELSRHPRAYT
 1051 NKRLAHLTVY YKLMARRAQV PSIKDRIPYV IVAQTREVEE TVARLAALRE
 1101 LDAAAPGDEP APPAALPSA KRPRETPSHA DPPGGASKPR KLLVSELAED
 50 1151 PGYAIARGVP LNTDYYFSLH LGAACVTFKA LFGNNAKITE SLLKRFPET
 1201 WHPPDDVAAR LRAAGFGPAG AGATAEETRR MLHRAFDTLA *

SEQ.ID.NO. 5 DNA sequence of DNA polymerase gene for HSV1-KOS-M1

1 ATGTTTTC CG GTGGCGGCGG CCCGCTGTCC CCCGGAGGAA AGTCGGCGGC
5 51 CAGGGCGGCG TCCGGGTTTT TTGCGCCCGC CGGCCCTCGC GGAGCCGGCC
101 GGGGACCCCC GCCTTGTTTG AGGCAAACT TTTACAACCC CTACCTCGCC
151 CCAGTCGGGA CGCAACAGAA GCCGACCGGG CCAACCCAGC GCCATACGTA
10 201 CTATAGCGAA TGCATGAAT TTCGATTCAT CGCCCCGCGG GTGCTGGACG
251 AGGATGCCCC CCCGGAGAAG CGCGCCGGGG TGCACGACGG TCACCTCAAG
15 301 CGCGCCCCCA AGGTGTACTG CGGGGGGGAC GAGCGCGACG TCCTCCGCGT
351 CGGGTCGGGC GGCTTCTGGC CGCGGCGCTC GCGCCTGTGG GGCGGCGTGG
401 ACCACGCCCC GGCGGGGTTT AACCCACCG TCACCGTCTT TCACGTGTAC
20 451 GACATCCTGG AGAACGTGGA GCACGCGTAC GGCATGCGCG CGGCCAGTT
501 CCACGCGCGG TTTATGGACG CCATCACACC GACGGGGACC GTCATCACGC
25 551 TCCTGGGCCT GACTCCGAA GGCCACCGGG TGGCCGTTCA CGTTTACGGC
601 ACGCGGCAGT ACTTTTACAT GAACAAGGAG GAGGTTGACA GGCACCTACA
651 ATGCCGCGCC CCACGAGATC TCTGCGAGCG CATGGCCGCG GCCCTGCGCG
30 701 AGTCCCCGGG CGCGTCGTT CGCGGCATCT CCGCGGACCA CTTCGAGGCG
751 GAGGTGGTGG AGCGCACC GAAGCGGGCG CGTGCTGTCT TACCTGTGCG
35 801 GTTTTACCGC GTCTACGTCC GAAGCGGGCG CGTGCTGTCT TACCTGTGCG
851 ACAACTTCTG CCCGGCCATC AAGAAGTACG AGGGTGGGGT CGACGCCACC
901 ACCCGGTTCA TCCTGGACAA CCGGGGTTT GTCACCTTCG GCTGGTACCG
40 951 TCTCAAACCG GGCCGGAACA ACACGCTAGC CCAGCCGCGG GCCCCGATGG
1001 CCTTCGGGAC ATCCAGCGAC GTCGAGTTTA ACTGTACGGC GGACAACCTG
45 1051 GCCATCGAGG GGGGCATGAG CGACCTACCG GCATACAAGC TCATGTGCTT
1101 CGATATCGAA TGCAAGGCGG GGGGGGAGGA CGAGCTGGCC TTTCCGGTGG
1151 CCGGGACCCC GGAGGACCTG GTTATTCAGA TATCCTGTCT GCTCTACGAC
50 1201 CTGTCCACCA CCGCCCTGGA GCACGTCTC CTGTTTTCGC TCGGTTCTG
1251 CGACCTCCCC GAATCCCACC TGAACGAGCT GGCGGCCAGG GGCCTGCCCA
55 1301 CGCCCGTGGT TCTGGAATTC GACAGCGAAT TCGAGATGCT GTTGGCCTTC
1351 ATGACCCTTG TGAAACAGTA CGGCCCCGAG TTCGTGACCG GGTACAACAT
1401 CATCAACTTC GACTGGCCCT TCTTGCTGGC CAAGTTGACG GACATTTACA
60

1451 AGGTCCCCCT GGACGGGTAC GGCCGCATGA ACGGCCGGGG CGTGTTTCGC
1501 GTGTGGGACA TAGGCCAGAG CCACTTCCAG AAGCGCAGCA AGATAAAGGT
5 1551 GAACGGCATG GTGAACATCG ACATGTACGG GATCATAACC GACAAGATCA
1601 AGCTCTCGAG CTACAAGCTC AACGCCGTGG CCGAAGCCGT CCTGAAGGAC
1651 AAGAAGAAGG ACCTGAGCTA TCGCGACATC CCCGCCTACT ACGCCGCCGG
10 1701 GCCCGCGCAA CGCGGGGTGA TCGCGAGTA CTGCATACAG GATTCCCTGC
1751 TGGTGGGCCA GCTGTTTTTT AAGTTTTTGC CCCATCTGGA GCTCTCGGCC
1801 GTCGCGCGCT TGGCGGGTAT TAACATCACC CGCACCATCT ACGACGGCCA
1851 GCAGATCCGC GTCTTTACGT GCCTGCTGCG CCTGGCCGAC CAGAAGGGCT
1901 TTATTCTGCC GGACACCCAG GGGCGATTTA GGGGCGCCGG GGGGGAGGCG
20 1951 CCCAAGCGTC CGGCCGAGC CCGGGAGGAC GAGGAGCGGC CAGAGGAGGA
2001 GGGGGAGGAC GAGGACGAAC GCGAGGAGGG CGGGGGCGAG CGGGAGCCGG
25 2051 AGGGCGCGCG GGAGACCGCC GGCCGGCACG TGGGGTACCA GGGGGCCAGG
2101 GTCCTTGACC CCACTTCCGG GTTTCACGTG AACCCCGTGG TGGTGTTCGA
2151 CTTTGCCAGC CTGTACCCCA GCATCATCCA GGCCACAAC CTGTGCTTCA
30 2201 GCACGCTCTC CCTGAGGGCC GACGCAGTGG CGCACCTGGA GGCGGGCAAG
2251 GACTACCTGG AGATCGAGGT GGGGGGGCGA CGGCTGTTCT TCGTCAAGGC
35 2301 TCACGTGCGA GAGAGCCTCC TCAGCATCCT CCTGCGGGAC TGGCTCGCCA
2351 TGCGAAAGCA GATCCGCTCG CGGATTCCCC AGAGCAGCCC CGAGGAGGCC
2401 GTGCTCCTGG ACAAGCAGCA GGCCGCCATC AAGGTCGTGT GTAACCTCGT
40 2451 GTACGGGTTC ACGGGAGCGC AGCACGGA CTGCGCGTGC CTGCACGTTG
2501 CCGCGACGGT GACGACCATC GGCCGCGAGA TGCTGCTCGC GACCCGCGAG
45 2551 TACGTCCACG CGCGCTGGGC GGCCTTCGAA CAGCTCCTGG CCGATTTCCT
2601 GGAGGCGGCC GACATGCGCG CCCCCGGGCC CTATTCCATG CGCATCATCT
2651 ACGGGGACAC GGA CTCCATA TTTGTGCTGT GCCGCGGCCT CACGGCCGCC
50 2701 GGGCTGACGG CCATGGGCGA CAAGATGGCG AGCCACATCT CGCGCGCGCT
2751 GTTTCTGCCC CCCATCAAAC TCGAGTGCGA AAAGACGTTC ACCAAGCTGC
55 2801 TGCTGATCGC CAAGAAAAAG TACATCGGCG TCATCTACGG GGGTAAGATG
2851 CTCATCAAGG GCGTGGATCT GGTGCGCAA AACA ACTGCG CGTTTATCAA
2901 CCGCACCTCC AGGGCCCTGG TCGACCTGCT GTTTTACGAC GATACCGTAT
60

2951 CCGGAGCGGC CGCCGCGTTA GCCGAGCGCC CCGCAGAGGA GTGGCTGGCG
3001 CGACCCCTGC CCGAGGGACT GCAGGCGTTC GGGGCCGTCC TCGTAGACGC
5 3051 CCATCGGCGC ATCACCGACC CGGAGAGGGA CATCCAGGAC TTTGTCCTCA
3101 CCGCCGAACT GAGCAGACAC CCGCGCGCGT ACACCAACAA GCGCCTGGCC
3151 CACCTGACGG TGTATTACAA GCTCATGGCC CGCCGCGCGC AGGTCCCCTC
10 3201 CATCAAGGAC CGGATCCCGT ACGTGATCGT GGCCCAGACC CGCGAGGTAG
3251 AGGAGACGGT CGCGCGGCTG GCCGCCCTCC GCGAGCTAGA CGCCGCCGCC
15 3301 CCAGGGGACG AGCCCGCCCC CCCC GCGGCC CTGCCCTCCC CGGCCAAGCG
3351 CCCCCGGGAG ACGCCGTCGC ATGCCGACCC CCCGGGAGGC GCGTCCAAGC
3401 CCCGCAAGCT GCTGGTGTCC GAGCTGGCCG AGGATCCCGC ATACGCCATT
20 3451 GCCCACGGCG TCGCCCTGAA CACGGACTAT TACTTCTCCC ACCTGTTGGG
3501 GGCGGCGTGC GTGACATTCA AGGCCCTGTT TGGGAATAAC GCCAAGATCA
25 3551 CCGAGAGTCT GTTAAAAAGG TTTATTCCCG AAGTGTGGCA CCCCCGGAC
3601 GACGTGGCCG CGCGGCTCCG GGCCGCAGGG TTCGGGGCGG TGGGTGCCGG
3651 CGCTACGGCG GAGGAAACTC GTCGAATGTT GCATAGAGCC TTTGATACTC
30 3701 TAGCATGA

SEQ.ID.NO. 6 Amino acid sequence of DNA polymerase for HSV1-KOS-M1

1 MFSGGGGPLS PGGKSAARAA SGFFAPAGPR GAGRGPPPCL RQNFYNPYLA
5 51 PVGTQQKPTG PTQRHTYYSE CDEFRIAPR VLDEDAPPEK RAGVHDGHLK
101 RAPKVYCGGD ERDVLRVGSG GFWPRRSRLW GGVDHAPAGF NPTVTVFHVY
10 151 DILENVEHAY GMRAAQFHAR FMDAITPTGT VITLLGLTPE GHRVAVHVY
201 TRQYFYMNKE EVDRHLQCRA PRDLCERMAA ALRESPGASF RGISADHFEA
251 EVVERTDVYY YETRPALFYR VYVRSGRVLS YLCDNFCPAI KKYEGGVDAT
15 301 TRFILDNPGF VTFGWYRLKP GRNNTLAQPR APMAFGTSSD VEFNCTADNL
351 AIEGGMSDLP AYKLMCFDIE CKAGGEDELA FPVAGHPEDL VIQISCLLYD
20 401 LSTTALEHVL LFSLGSCDLP ESHLNELAAR GLPTPVVLEF DSEFEMLLAF
451 MTLVKQYGPE FVTGYNINF DWPFLAKLT DIYKVPLDGY GRMNGRGVFR
501 VWDIGQSHFQ KRSKIKVNGM VNIDMYGIIT DKIKLSSYKL NAVAEAVLKD
25 551 KKKDLSYRDI PAYYAAGPAQ RGVIGEYCIQ DSLLVGQLFF KFLPHLELSA
601 VARLAGINIT RTIYDGQQIR VFTCLRLAD QKGFILPDTQ GRFRGAGGEA
30 651 PKRPAAARED EERPEEEGED EDEREEGGGE REPEGARETA GRHVGYYQGAR
701 VLDPTSGFHV NPVVVFDFAS LYPSTQAHN LCFSTLSLRA DAVAHLEAGK
751 DYLEIEVGGR RLFFVKAHVR ESLLSILLRD WLAMRKQIRS RIPQSSPEEA
35 801 VLLDKQAAI KVV CNSVYGF TGAQHGLLPC LHVAATVTI GREMLLATRE
851 YVHARWAAFE QLLADFFPEAA DMRAPGPYSM RIYGD TDSI FVLCRGLTAA
40 901 GLTAMGDKMA SHISRALFLP PIKLECEKTF TKLLLIAKKK YIGVIYGGKM
951 LIKGVDLVRK NNCAFINRTS RALVDLLFYD DTVSGAAAAL AERPABEWLA
1001 RPLPEGLQAF GAVLVDAHRR ITDPERDIQD FVLTAELSRH PRAYTNKRLA
45 1051 HLTVYYKLMA RRAQVPSIKD RIPPVIVAQT REVEETVARL AALRELDAAA
1101 PGDEPAPPAA LPSPAKRPRE TPSHADPPGG ASKPRKLLVS ELAEDPAYAI
50 1151 AHGVALNTDY YFSHLLGAAC VTFKALFGNN AKITESLLKR FIPEVWHPPD
1201 DVAARLRAAG FGAVGAGATA EETRRMLHRA FDTLA*

SEQ.ID.NO. 7 **DNA sequence of HSV polymerase gene for HSV1-F-M1**

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5      1  ATGTTTTC CG GTGGCGGCGG CCCGCTGTCC CCCGGAGGAA AGTCGGCGGC
      51  CAGGGCGGCG TCCGGGTTTT TTGCGCCCGC CGGCCCTCGC GGAGCCGGCC
     101  GGGGACCCCC GCCTTGCTTG AGGCAAACT TTTACAACCC CTACCTCGCC
     150  151  CCAGTCGGGA CGCAACAGAA GCCGACCGGG CCAACCCAGC GCCATACGTA
     200  201  CTATAGCGAA TGCGATGAAT TTCGATTCAT CGCCCCGCGG GTGCTGGACG
     250  251  AGGATGCCCC CCCGGAGAAG CGCGCCGGGG TGCACGACGG TCACCTCAAG
     300  301  CGCGCCCCCA AGGTGTACTG CGGGGGGGAC GAGCGCGACG TCCTCCGCGT
     350  351  CGGGTCGGGC GGCTTCTGGC CGCGGCGCTC GCGCCTGTGG GGCGGCGTGG
     400  401  ACCACGCCCC GCGGGGGTTC AACCCACCG TCACCGTCTT TCACGTGTAC
     450  451  GACATCCTGG AGAACGTGGA GCACGCGTAC GGCATGCGCG CGGCCAGTT
     500  501  CCACGCGCGG TTTATGGACG CCATCACACC GACGGGGACC GTCATCACGC
     550  551  TCCTGGGCCT GACTCCGGA GGCCACCGGG TGGCCGTTCA CGTTTACGGC
     600  601  ACGCGGCAGT ACTTTTACAT GAACAAGGAG GAGGTCGACA GGCACCTACA
     650  651  ATGCCGCGCC CCACGAGATC TCTGCGAGCG CATGGCCGCG GCCCTGCGCG
     700  701  AGTCCCCGGG CGCGTCGTTC CGCGGCATTT CCGCGGACCA CTTCGAGGCG
     750  751  GAGGTGGTGG AGCGCACC GAAGCGGGCG CGTGCTGTCT TACCTGTGCG
     800  801  GTTTTACCGC GTCTACGTCC GAAGCGGGCG CGTGCTGTCT TACCTGTGCG
     850  851  ACAACTTCTG CCCGGCCATC AAGAAGTACG AGGGTGGGGT CGACGCCACC
     900  901  ACCCGGTTCA TCCTGGACAA CCCCGGGTTC GTCACCTTCG GCTGGTACCG
     950  951  TCTCAAACCG GGCCGGAACA ACACGCTAGC CCAGCCGCGG GCGCCGATGG
    1000 1001  CCTTCGGGAC ATCCAGCGAC GTCGAGTTTA ACTGTACGGC GGACAACCTG
    1050 1051  GCCATCGAGG GGGGCATGAG CGACCTACCG GCATACAAGC TCATGTGCTT
    1100 1101  CGATATCGAA TGCAAGGCGG GGGGGGAGGA CGAGCTGGCC TTTCCGGTGG
    1150 1151  CCGGGCACCC GGAGGACCTG GTCATCCAGA TATCCTGTCT GCTCTACGAC
    1200 1201  CTGTCCACCA CCGCCCTGGA GCACGTCTC CTGTTTTCGC TCGGTTCTCTG
    1250 1251  CGACCTCCCC GAATCCCACC TGAACGAGCT GGCGGCCAGG GGCCTGCCCA
    1300 1301  CGCCCGTGGT TCTGGAATTC GACAGCGAAT TCGAGATGCT GTTGGCCTTC
    1350 1351  ATGACCCTTG TGAAACAGTA CGGCCCGGAG TTCGTGACCG GGTACAACAT
    1400 1401  CATCAACTTC GACTGGCCCT TCTTGCTGGC CAAGCTGACG GACATTTACA
    1450 1451  AGGTCCCCCT GGACGGGTAC GGCCGCATGA ACGGCCGGGG CGTGTTTCGC
    1500 1501  GTGTGGGACA TAGGCCAGAG CCACTTCCAG AAGCGCAGCA AGATAAAGGT
    1550 1551  GAACGGCATG GTGAACATCG ACATGTACGG GATTATAACC GACAAGATCA

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1601 AGCTCTCGAG CTACAAGCTC AACGCCGTGG CCGAAGCCGT CCTGAAGGAC
 1651 AAGAAGAAGG ACCTGAGCTA TCGCGACATC CCCGCCTACT ACGCCGCCGG
 5 1701 GCCCGCGCAA CGCGGGGTGA TCGGCGAGTA CTGCATACAG GATTCCCTGC
 1751 TGGTGGGCCA GCTGTTTTTT AAGTTTTTGC CCCATCTGGA GCTCTCGGCC
 10 1801 GTCGCGCGCT TGGCGGGTAT TAACATCACC CGCACCATCT ACGACGGCCA
 1851 GCAGATCCGC GTCTTTACGT GCCTGCTGCG CCTGGCCGAC CAGAAGGGCT
 1901 TTATTCTGCC GGACACCCAG GGGCGATTTA GGGGCGGCGG GGGGGAGGCG
 15 1951 CCCAAGCGTC CGGCCGCAGC CCGGGAGGAC GAGGAGCGGC CAGAGGAGGA
 2001 GGGGGAGGAC GAGGACGAAC GCGAGGAGGG CGGGGGCGAG CGGGAGCCGG
 20 2051 AGGGCGCGCG GGAGACCGCC GGCCGGCACG TGGGGTACCA GGGGGCCAGG
 2101 GTCCTTGACC CCACTTCCGG GTTTCATGTG AACCCCGTGG TGGTGTTCGA
 2151 CTTTGCCAGC CTGTACCCCA GCATCATCCA GGCCACAAC CTGTGCTTCA
 25 2201 GCACGCTCTC CCTGAGGGCC GACGCAGTGG CGCACCTGGA GGCGGGCAAG
 2251 GACTACCTGG AGATCGAGGT GGGGGGGCGA CGGCTGTTCT TCGTCAAGGC
 30 2301 TCACGTGCGA GAGAGCCTCC TCAGCATCCT CCTGCGGGAC TGGCTCGCCA
 2351 TGCAGAAAGCA GATCCGCTCG CGGATTCCCC AGAGCAGCCC CGAGGAGGCC
 2401 GTGCTCCTGG ACAAGCAGCA GGCCGCCATC AAGGTCGTGT GTAACTCGGT
 35 2451 TTACGGGTTC ACGGGAGCGC AGCACGGA CTGCGCGTGC CTGCACGTTG
 2501 CCGCGACGGT GACGACCATC GGCCGCGAGA TGCTGCTCGC GACCCGCGAG
 40 2551 TACGTCCACG CGCGCTGGGC GGCCTTCGAA CAGCTCCTGG CCGATTTCCC
 2601 GGAGGCGGCC GACATGCGCG CCCCCGGGCC CTATTCCATG CGCATCATCT
 2651 ACGGGGACAC GGACTCCATC TTTGTGCTGT GCCGCGGCCT CACGGCCGCC
 45 2701 GGGCTGACGG CCGTGGGCGA CAAGATGGCG AGCCACATCT CGCGCGCGCT
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 50 2801 TGCTGATCGC CAAGAAAAAG TACATCGGCG TCATCTACGG GGGTAAGATG
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 55 2951 CCGGAGCGGC CGCCGCGTTA GCCGAGCGCC CCGCAGAGGA GTGGCTGGCG
 3001 CGACCCCTGC CCGAGGGACT GCAGGCGTTC GGGGCCGTCC TCGTAGACGC
 60 3051 CCATCGGCGC ATCACCACC CGGAGAGGGA CATCCAGGAC TTTGTCTCTA
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 3151 CACCTGACGG TGTATTACAA GCTCATGGCC CGCCGCGCGC AGGTCCCGTC
 65 3201 CATCAAGGAC CGGATCCCGT ACGTGATCGT GGCCAGACC CGCGAGGTAG

3251 AGGAGACGGT CGCGCGGCTG GCCGCCCTCC GCGAGCTCGA CGCCGCCGCC
3301 CCAGGGGACG AGCCCGCCCC CCCC GCGGCC CTGCCCTCCC CGGCCAAGCG
5 3351 CCCCCGGGAG ACGCCGTTGC ATGCCGACCC CCCGGGAGGC GCGTCCAAGC
3401 CCCGCAAGCT GCTGGTGTCC GAGCTGGCCG AGGATCCCCG ATACGCCATT
3451 GCCCACGGCG TCGCCCTGAA CACGGACTAT TACTTCTCCC ACCTGTTGGG
10 3501 GGCGGCGTGC GTGACATTCA AGGCCCTGTT TGGGAATAAC GCCAAGATCA
3551 CCGAGAGTCT GTTAAAAAGG TTTATTCCCG AAGTGTGGCA CCCCCCGAC
15 3601 GACGTGGCCG CGCGGCTCCG GGCCGCAGGG TTCGGGGCGG TGGGTGCCGG
3651 CGCTACGGCG GAGGAAACTC GTCGAATGTT GCATAGAGCC TTTGATACTC
3701 TAGCATGA

SEQ.ID.NO. 8 Amino acid sequence of DNA polymerase for HSV1-F-M1

1 MFSGGGGPLS PGGKSAARAA SGFFAPAGPR GAGRGPPPCL RQNFYNPYLA
5 51 PVGTQQKPTG PTQRHTYYSE CDEFRIAPR VLDEDAPPEK RAGVHDGHLK
101 RAPKVYCGGD ERDVLRVGSG GFWPRRSRLW GGVDHAPAGF NPTVTVFHVY
151 DILENVEHAY GMRAAQFHAR FMDAITPTGT VITLLGLTPE GHRVAVHVY
10 201 TRQYFYMNKE EVDRHLQCRA PRDLCERMAA ALRESPGASF RGISADHFEA
251 EVVERTDVYY YETRPALFYR VYVRSGRVLS YLCDNFPAI KKYEGGVDAT
15 301 TRFILDNPGF VTFGWYRLKP GRNNTLAQPR APMAFGTSSD VEFNCTADNL
351 AIEGGMSDLP AYKLMCFDIE CKAGGEDELA FPVAGHPEDL VIQISCLLYD
401 LSTTALEHVL LFSLGSCDLP ESHLNELAAR GLPTPVVLEF DSEFEMLLAF
20 451 MTLVKQYGPE FVTGYNIINF DWPFLAKLT DIYKVPLDGY GRMNGRGVFR
501 VWDIGQSHFQ KRSKIKVNGM VNIDMYGIIT DKIKLSSYKL NAVAEAVLKD
25 551 KKKDLSYRDI PAYYAAGPAQ RGVIGEYCIQ DSLLVGQLFF KFLPHLELSA
601 VARLAGINIT RTTYDGQQR VFTCLRLAD QKGFILPDTQ GRFRGGGGEA
651 PKRPAAARED EERPEEEGED EDERBEGGGE REPEGARETA GRHVG YQGAR
30 701 VLDPTSGFHV NPVVVDFDAS LYPSIIQAHN LCFSTLSLRA DAVAHLEAGK
751 DYLEIEVGGR RLFFVKAHVR ESLLSILLRD WLAMRKQIRS RIPQSSPEEA
35 801 VLLDKQAAI KVV CNSVYGF TGAQHGLLPC LHVAATVTTI GREMLLATRE
851 YVHARWAAFE QLLADFPEAA DMRAPGPYSM RIYGD TDSI FVLCRGLTAA
901 GLTAVGDKMA SHISRALFLS PIKLECEKTF TKLLLIAKKK YIGVIYGGKM
40 951 LIKGVDLVRK NNCAFINRTS RALVDLLFYD DTVSGAAAAL AERPAAEWLA
1001 RPLPEGLQAF GAVLVDAHRR ITDPERDIQD FVLTAE LSRH PRAYTNKRLA
45 1051 HLTVYYKLMA RRAQVPSIKD RPYVIVAQT REVEETVARL AALRELDAAA
1101 PGDEPAPPAA LPSPAKRPRE TPLHADPPGG ASKPRKLLVS ELAEDPAYAI
1151 AHGVALNTDY YFSHLLGAAC VTFKALFGNN AKITESLLKR FIPEVWHPPD
50 1201 DVAARLRAAG FGAVGAGATA EETRMLHRA FDTLA*

SEQ.ID.NO. 9 DNA sequence of HSV polymerase gene for HSV1-DJL-M1

1 ATGTTTTCCG GTGGCGGCGG CCCGCTGTCC CCCGGAGGAA AGTCGGCGGC
5 51 CAGGGCGGCG TCCGGGTTTT TTGCGCCCGC CGGCCCTCGC GGAGCCGGCC
101 GGGGACCCCC GCCTTGTTTG AGGCAAACT TTTACAACCC CTACCTCGCC
151 CCAGTCGGGA CGCAACAGAA GCCGACCGGG CCAACCCAGC GCCATACGTA
10 201 CTATAGCGAA TCGATGAAT TTCGATTCAT CGCCCCGCGG GTGCTGGACG
251 AGGATGCCCC CCCGGAGAAG CGCGCCGGGG TGCACGACGG TCACCTCAAG
15 301 CGCGCCCCCA AGGTGTACTG CGGGGGGGAC GAGCGCGACG TCCTCCGCGT
351 CGGGTCGGGC GGCTTCTGGC CGCGGCGCTC GCGCCTGTGG GGCGGCGTGG
401 ACCACGCCCC GGCGGGGTTC AACCCACCG TCACCGTCTT TCACGTGTAT
20 451 GACATCCTGG AGAACGTGGA GCACGCGTAC GGCATGCGCG CGGCCAGTT
501 CCACGCGCGG TTTATGGACG CCATCACACC GACGGGGACC GTCATCACGC
25 551 TCCTGGGCCT GACTCCGGAA GGCCACCGGG TGGCCGTTCA CGTTTACGGC
601 ACGCGGCAGT ACTTTTACAT GAACAAGGAG GAGGTTGACA GGCACCTACA
651 ATGCCGCGCC CCACGAGATC TCTGCGAGCG CATGGCCGCG GCCCTGCGCG
30 701 AGTCCCCGGG CGCGTCGTTC CGCGGCATCT CCGCGGACCA CTTGAGGGCG
751 GAGGTGGTGG AGCGCACC GAAGCGGGCG CGTGCTGTGCG TACCTGTGCG
35 801 GTTTTACCGC GTCTACGTCC GAAGCGGGCG CGTGCTGTGCG TACCTGTGCG
851 ACAACTTCTG CCCGGCCATC AAGAAGTACG AGGGTGGGGT CGACGCCACC
901 ACCCGGTTCA TCCTGGACAA CCCCAGGTTC GTCACCTTCG GCTGGTACCG
40 951 TCTCAAACCG GGCCGGAACA ACACGCTAGC CCAGCCGCGG GCCCCGATGG
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50 1201 CTGTCCACCA CCGCCCTGGA GCACGTCTC CTGTTTTCGC TCGGTTCTTG
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55 1301 CGCCCGTGGT TCTGGAATTC GACAGCGAAT TCGAGATGCT GTTGGCCTTC
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1451 AGGTCCCCCT GGACGGGTAC GGCCGCATGA ACGGCCGGGG CGTGTTTCGC
1501 GTGTGGGACA TAGGCCAGAG CCACTTCCAG AAGCGCAGCA AGATAAAGGT
5 1551 GAACGGCATG GTGAACATCG ACATGTACGG GATTATAACC GACAAGATCA
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15 1801 GTCGCGCGCT TGGCGGGTAT TAACATCACC CGCACCATCT ACGACGGCCA
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1951 CCAAGCGTC CGGCCGAGC CCGGGAGGAC GAGGAGCGGC CAGAGGAGGA
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25 2051 AGGGCGCGCG GGAGACCGCC GGCCGGCACG TGGGGTACCA GGGGGCCAGG
2101 GTCCTTGACC CCACTTCCGG GTTTCACGTG AACCCCGTGG TGGTGTTCTGA
30 2151 CTTTGCCAGC CTGTACCCCA GCATCATCCA GGCCACAAC CTGTGCTTCA
2201 GCACGCTCTC CCTGAGGGCC GACGCAGTGG CGCACCTGGA GGCGGGCAAG
2251 GACTACCTGG AGATCGAGGT GGGGGGGCGA CGGCTGTTCT TCGTCAAGGC
35 2301 TCACGTGCGA GAGAGCCTCC TCAGCATCCT CCTGCGGGAC TGGCTCGCCA
2351 TCGCAAAGCA GATCCGCTCG CGGATTCCCC AGAGCAGCCC CGAGGAGGCC
40 2401 GTGCTCCTGG ACAAGCAGCA GGCCGCCATC AAGGTCGTGT GTAACTCGGT
2451 TTACGGGTTC ACGGGAGCGC AGCACGGACT CCTGCCGTGC CTGCACGTTG
2501 CCGCGACGGT GACGACCATC GGCCGCGAGA TGCTGCTCGC GACCCGCGAG
45 2551 TACGTCCACG CGCGCTGGGC GGCCTTCGAA CAGCTCCTGG CCGATTCCCC
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50 2651 ACGGGGACAC GGAATCCATA TTTGTGCTGT GCCGCGGCCT CACGGCCGCC
2701 GGGCTGACGG CCGTGGGCGA CAAGATGGCG AGCCACATCT CGCGCGCGCT
2751 GTTTCTGCCC CCCATCAAAC TCGAGTGCGA AAAGACGTTC ACCAAGCTGC
55 2801 TGCTGATCGC CAAGAAAAAG TACATCGGCG TCATCTACGG GGGTAAGATG
2851 CTCATCAAGG GCGTGGATCT GGTGCGCAAA AACAACTGCG CGTTTATCAA
60 2901 CCGCACCTCC AGGGCCCTGG TCGACCTGCT GTTTTACGAC GATACCGTAT

2951 CCGGAGCGGC CGCCGCGTTA GCCGAGCGCC CCGCAGAGGA GTGGCTGGCG
3001 CGACCCCTGC CCGAGGGACT GCAGGCGTTC GGGGCCGTCC TCGTAGACGC
5 3051 CCATCGGCGC ATCACCGACC CGGAGAGGGA CATCCAGGAC TTTGTTCTCA
3101 CCGCCGAACT GAGCAGACAC CCGCGCGCGT ACACCAACAA GCGCCTGGCC
10 3151 CACCTGACGG TGTATTACAA GTCATGGCC CGCCGCGCGC AGGTCCCGTC
3201 CATCAAGGAC CGGATCCCGT ACGTGATCGT GGCCAGACC CGCGAGGTAG
3251 AGGAGACGGT CGCGCGGCTG GCCGCCCTCC GCGAGCTAGA CGCCGCCGCC
15 3301 CCAGGGGACG AGCCCGCCCC CCGCGGGCC CTGCCCTCCC CGGCCAAGCG
3351 CCCCCGGGAG ACGCCGTCGC CTGCCGACCC CCGGGAGGC GCGTCCAAGC
20 3401 CCCGCAAGCT GCTGGTGTCC GAGCTGGCCG AGGATCCCGC ATACGCCATT
3451 GCCCACGGCG TCGCCCTGAA CACGGACTAT TACTTCTCCC ACCTGTTGGG
3501 GCGGGCGTGC GTGACATTCA AGGCCCTGTT TGGGAATAAC GCCAAGATCA
25 3551 CCGAGAGTCT GTTAAAAAGG TTTATTCCCG AAGTGTGGCA CCCCCGGAC
3601 GACGTGGCCG CGCGGCTCCG GACCGCAGGG TTCGGGGCGG TGGGTGCCGG
30 3651 CGCTACGGCG GAGGAAACTC GTCGAATGTT GCATAGAGCC TTTGATACTC
3701 TAGCATGA

SEQ.ID.NO. 10 Amino acid sequence of DNA polymerase for HSV1-DJL-M1

1 MFSGGGGGLS PGGKSAARAA SGFFAPAGPR GAGRGPPPCL RQNFYNPYLA
5 51 PVGTQQKPTG PTQRHTYYSE CDEFRFIAPR VLDEDAPPEK RAGVHDGHLK
101 RAPKVYCGGD ERDVLRVGSG GFWPRRSRLW GGVDHAPAGF NPTVTVFHVY
151 DILENVEHAY GMRAAQFHAR FMDAITPTGT VITLLGLTPE GHRVAVHVY
10 201 TRQYFYMNKE EVDRHLQCRA PRDLCERMAA ALRESPGASF RGISADHFEA
251 EVVERTDVYY YETRPALFYR VYVRSGRVLS YLCDNFCPAI KKYEGGVDAT
15 301 TRFILDNPGF VTFGWYRLKP GRNNTLAQPR APMAFGTSSD VEFNCTADNL
351 AIEGGMSDLP AYKLMCFDIE CKAGGEDELA FPVAGHPEDL VIQISCLLYD
401 LSTTALEHVL LFSLGSCDLP ESHLNELAAR GLPTPVVLEF DSEFEMLLAF
20 451 MTLVKQYGPE FVTGYNIINF DWPFLAKLT DIYKVPLDGY GRMNGRGVFR
501 VWDIGQSHFQ KRSKIKVNGM VNIDMYGIIT DKIKLSSYKL NAVA EAVLKD
25 551 KKKDLSYRDI PTYYAAGPAQ RGVIGEYCIQ DSSLVGQLFF KFLPHLELSA
601 VARLAGINIT RTIYDGQQIR VFTCLRLAD QKGFILPDTQ GRFRGAGGEA
651 PKRPAAARED EERPEEEGED ENERE EGGGE REPEGARETA GRHVG YQGAR
30 701 VLDPTSGFHV NPVVVFDFAS LYP SIIQAHN LCFSTLSLRA DAVAHLEAGK
751 DYLEIEVGGR RLFFVKAHVR ESLLSILLRD WLAMRKQIRS RIPQSSPEEA
35 801 VLLDKQAAI KVCNSVYGF TGAQHGLLPC LHVAATVTI GREMLLATRE
851 YVHARWAAFE QLLADFPEAA DMRAPGPYSM RIYGD TDSI FVLCRGLTAA
901 GLTAVGDKMA SHISRALFLP PIKLECEKTF TKLLLIAKKK YIGVIYGGKM
40 951 LIKGVDLVRK NNCAFINRTS RALVDLLFYD DTVSGAAAAL AERP AEEWLA
1001 RPLPEGLQAF GAVLVDAHRR ITDPERDIQD FVLTAELSRH PRAYTNKRLA
45 1051 HLTVYYKLMA RRAQVPSIKD RPYVIVAQT REVEETVARL AALRELDAAA
1101 PGDEPAPPAA LPSPAKRPRE TPSPADPPGG ASKPRKLLVS ELAEDPAYAI
1151 AHGVALNTDY YFSHLLGAAC VTFKALFGNN AKITESLLKR FIPEVWHPPD
50 1201 DVAARLRTAG FGAVGAGATA EETRMLHRA FDTLA*

SEQ.ID.NO. 11 DNA sequence of DNA polymerase gene for HMCV-AD169-M1

1 ATGTTTTTCA ACCCGTATCT GAGCGGCGGC GTGACCGGCG GTGCGGTTCG
5 51 GGGTGGCCGG CGTCAGCGTT CGCAGCCCGG CTCCGCGCAG GGCTCGGGCA
101 AGCGGCCGCC ACAGAAACAG TTTTTCGAGA TCGTGCCGCG AGGTGTCATG
151 TTCGACGGTC AGACGGGGTT GATCAAGCAT AAGACGGGAC GGCTGCCTCT
10 201 CATGTTCTAT CGAGAGATTA AACATTTGTT GAGTCATGAC ATGGTTTGGC
251 CGTGTCCTTG GCGCGAGACC CTGGTGGGTC GCGTGGTGGG ACCTATTTCG
15 301 TTTCACACCT ACGATCAGAC GGACGCCGTG CTCTTCTTCG ACTCGCCCGA
351 AAACGTGTCG CCGCGCTATC GTCAGCATCT GGTGCCTTCG GGGAACGTGT
401 TCGTTTTCTT CGGGGCCACA GAACACGGCT ACAGTATCTG CGTCAACGTT
20 451 TTCGGGCAGC GCAGCTACTT TTA CTGTGAG TACAGCGACA CCGATAGGCT
501 GCGTGAGGTC ATTGCCAGCG TGGGCGAACT AGTGCCCGAA CCGCGGACGC
25 551 CATACGCCGT GTCTGTCACG CCGGCCACCA AGACCTCCAT CTATGGGTAC
601 GGGACGCGAC CCGTGCCCGA TTTGCAGTGT GTGTCTATCA GCAACTGGAC
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35 801 TCGCGCGTCG ACTTGTGATA TCGAGGTAGA CTGCGATGTC TCTGACCTGG
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50 1201 CCGGCCTTTG TGACCGGTTA CAACATCAAC TCTTTTGA CT TGAAGTACAT
1251 CCTCACGCGT CTCGAGTACC TGTATAAGGT GGA CTGCGAG CGCTTCTGCA
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5 1551 TTACAAGGAC ATCCCGCGTT GTTTCGTGGC TAATGCCGAG GGCCGCGCCC
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10 1651 AACACCATTA ATTTTCACTA CGAGGCCGGG GCCATCGCGC GGCTGGCTAA
1701 AATTCCGTTG CGGCGTGTCA TCTTTGACGG ACAGCAGATC CGTATCTACA
1751 CCTCGCTGCT GGACGAGTGC GCCTGCCGCG ATTTTATCCT GCCCAACCAC
15 1801 TACAGCAAAG GTACGACGGT GCCCCGAAACG AATAGCGTTG CTGTGTCACC
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20 1901 TGGCGGCTAT GTTTCAGATG TCGCCGCCCT TGCAATCTGC GCCGTCCAGT
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SEQ. ID. NO. 12 Amino acid sequence of DNA polymerase for HCMV-AD169-M1

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50 1151 GEPAKKRARK PPSAVCNYEV AEDPSYVREH GVPIHADKYF EQVLKAVTNV
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Figure 6
SEQ.ID.NO.13 **Amino acid sequence of DNA polymerase for HCMV-AD169**

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SEQUENCE LISTING

<110> Homa, Fred
 Wathen, Michael
 Hopkins, Todd
 Thomsen, Darrell

<120> A Method for Treating Herpes Virus

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<170> PatentIn version 3.0

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 <212> PRT
 <213> herpes simplex

<400> 4

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 35 40 45
 His Leu Ala Gln Thr Gly Thr Gln Pro Lys Ala Pro Gly Pro Ala Gln
 50 55 60
 Arg His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro
 65 70 75 80
 Arg Ser Leu Asp Glu Asp Ala Pro Ala Glu Gln Arg Thr Gly Val His
 85 90 95
 Asp Gly Arg Leu Arg Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu
 100 105 110
 Arg Asp Val Leu Arg Val Gly Pro Glu Gly Phe Trp Pro Arg Arg Leu
 115 120 125
 Arg Leu Trp Gly Gly Ala Asp His Ala Pro Glu Gly Phe Asp Pro Thr
 130 135 140
 Val Thr Val Phe His Val Tyr Asp Ile Leu Glu His Val Glu His Ala

145		150		155		160
Tyr Ser Met Arg	Ala Ala Gln Leu His	Glu Arg Phe Met Asp	Ala Ile			
	165	170	175			
Thr Pro Ala Gly	Thr Val Ile Thr	Leu Leu Gly Leu Thr	Pro Glu Gly			
	180	185	190			
His Arg Val Ala	Val His Val Tyr	Gly Thr Arg Gln Tyr	Phe Tyr Met			
	195	200	205			
Asn Lys Ala Glu	Val Asp Arg His	Leu Gln Cys Arg	Ala Pro Arg Asp			
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Leu Cys Glu Arg	Leu Ala Ala Ala	Leu Arg Glu Ser	Pro Gly Ala Ser			
	225	230	235			240
Phe Arg Gly Ile	Ser Ala Asp His	Phe Glu Ala Glu	Val Val Glu Arg			
	245	250	255			
Ala Asp Val Tyr	Tyr Tyr Glu Thr	Arg Pro Thr Leu	Tyr Tyr Arg Val			
	260	265	270			
Phe Val Arg Ser	Gly Arg Ala Leu	Ala Tyr Leu Cys	Asp Asn Phe Cys			
	275	280	285			
Pro Ala Ile Arg	Lys Tyr Glu Gly	Gly Val Asp Ala	Thr Thr Arg Phe			
	290	295	300			
Ile Leu Asp Asn	Pro Gly Phe Val	Thr Phe Gly Trp	Tyr Arg Leu Lys			
	305	310	315			320
Pro Gly Arg Gly	Asn Ala Pro Ala	Gln Pro Arg Pro	Pro Thr Ala Phe			
	325	330	335			
Gly Thr Ser Ser	Asp Val Glu Phe	Asn Cys Thr Ala	Asp Asn Leu Ala			
	340	345	350			
Val Glu Gly Ala	Met Cys Asp Leu	Pro Ala Tyr Lys	Leu Met Cys Phe			
	355	360	365			
Asp Ile Glu Cys	Lys Ala Gly Gly	Glu Asp Glu Leu	Ala Phe Pro Val			
	370	375	380			
Ala Glu Arg Pro	Glu Asp Leu Val	Ile Gln Ile Ser	Cys Leu Leu Tyr			
	385	390	395			400
Asp Leu Ser Thr	Thr Ala Leu Glu	His Ile Leu Leu	Phe Ser Leu Gly			
	405	410	415			
Ser Cys Asp Leu	Pro Glu Ser His	Leu Ser Asp Leu	Ala Ser Arg Gly			
	420	425	430			
Leu Pro Ala Pro	Val Val Leu Glu	Phe Asp Ser Glu	Phe Glu Met Leu			
	435	440	445			
Leu Ala Phe Met	Thr Phe Val Lys	Gln Tyr Gly Pro	Glu Phe Val Thr			
	450	455	460			
Gly Tyr Asn Ile	Ile Asn Phe Asp	Trp Pro Phe Val	Leu Thr Lys Leu			
	465	470	475			480

Thr Glu Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly
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 Arg Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys
 500 505 510
 Arg Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly
 515 520 525
 Ile Ile Thr Asp Lys Val Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val
 530 535 540
 Ala Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp
 545 550 555 560
 Ile Pro Ala Tyr Tyr Ala Ser Gly Pro Ala Gln Arg Gly Val Ile Gly
 565 570 575
 Glu Tyr Cys Val Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys
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 Phe Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile
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 Asn Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr
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 Cys Leu Leu Arg Leu Ala Gly Gln Lys Gly Phe Ile Leu Pro Asp Thr
 625 630 635 640
 Gln Gly Arg Phe Arg Gly Leu Asp Lys Glu Ala Pro Lys Arg Pro Ala
 645 650 655
 Val Pro Arg Gly Glu Gly Glu Arg Pro Gly Asp Gly Asn Gly Asp Glu
 660 665 670
 Asp Lys Asp Asp Asp Glu Asp Gly Asp Glu Asp Gly Asp Glu Arg Glu
 675 680 685
 Glu Val Ala Arg Glu Thr Gly Gly Arg His Val Gly Tyr Gln Gly Ala
 690 695 700
 Arg Val Leu Asp Pro Thr Ser Gly Phe His Val Asp Pro Val Val Val
 705 710 715 720
 Phe Asp Phe Ala Ser Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu
 725 730 735
 Cys Phe Ser Thr Leu Ser Leu Arg Pro Glu Ala Val Ala His Leu Glu
 740 745 750
 Ala Asp Arg Asp Tyr Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe
 755 760 765
 Phe Val Lys Ala His Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg
 770 775 780
 Asp Trp Leu Ala Met Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser
 785 790 795 800
 Pro Pro Glu Glu Ala Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys
 805 810 815

Val Val Cys Asn Ser Val Tyr Gly Phe Thr Gly Ala Gln His Gly Leu
 820 825 830
 Leu Pro Cys Leu His Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu
 835 840 845
 Met Leu Leu Ala Thr Arg Ala Tyr Val His Ala Arg Trp Ala Glu Phe
 850 855 860
 Asp Gln Leu Leu Ala Asp Phe Pro Glu Ala Ala Gly Met Arg Ala Pro
 865 870 875 880
 Gly Pro Tyr Ser Met Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe
 885 890 895
 Val Leu Cys Arg Gly Leu Thr Ala Ala Gly Leu Val Ala Met Gly Asp
 900 905 910
 Lys Met Ala Ser His Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys
 915 920 925
 Leu Glu Cys Glu Lys Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys
 930 935 940
 Lys Tyr Ile Gly Val Ile Cys Gly Gly Lys Met Leu Ile Lys Gly Val
 945 950 955 960
 Asp Leu Val Arg Lys Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg
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 Ala Leu Val Asp Leu Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala
 980 985 990
 Ala Ala Leu Ala Glu Arg Pro Ala Glu Glu Trp Leu Ala Arg Pro Leu
 995 1000 1005
 Pro Glu Gly Leu Gln Ala Phe Gly Ala Val Leu Val Asp Ala His
 1010 1015 1020
 Arg Arg Ile Thr Asp Pro Glu Arg Asp Ile Gln Asp Phe Val Leu
 1025 1030 1035
 Thr Ala Glu Leu Ser Arg His Pro Arg Ala Tyr Thr Asn Lys Arg
 1040 1045 1050
 Leu Ala His Leu Thr Val Tyr Tyr Lys Leu Met Ala Arg Arg Ala
 1055 1060 1065
 Gln Val Pro Ser Ile Lys Asp Arg Ile Pro Tyr Val Ile Val Ala
 1070 1075 1080
 Gln Thr Arg Glu Val Glu Glu Thr Val Ala Arg Leu Ala Ala Leu
 1085 1090 1095
 Arg Glu Leu Asp Ala Ala Ala Pro Gly Asp Glu Pro Ala Pro Pro
 1100 1105 1110
 Ala Ala Leu Pro Ser Pro Ala Lys Arg Pro Arg Glu Thr Pro Ser
 1115 1120 1125
 His Ala Asp Pro Pro Gly Gly Ala Ser Lys Pro Arg Lys Leu Leu

1130	1135	1140
Val Ser Glu Leu Ala Glu Asp Pro Gly Tyr Ala Ile Ala Arg Gly		
1145	1150	1155
Val Pro Leu Asn Thr Asp Tyr Tyr Phe Ser His Leu Leu Gly Ala		
1160	1165	1170
Ala Cys Val Thr Phe Lys Ala Leu Phe Gly Asn Asn Ala Lys Ile		
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Thr Glu Ser Leu Leu Lys Arg Phe Ile Pro Glu Thr Trp His Pro		
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Pro Asp Asp Val Ala Ala Arg Leu Arg Ala Ala Gly Phe Gly Pro		
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Arg Ala Phe Asp Thr Leu Ala		
1235	1240	

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 <212> DNA
 <213> herpes simplex

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<212> PRT
<213> herpes simplex

<400> 6

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35 40 45
Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg
50 55 60
His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg
65 70 75 80
Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp
85 90 95
Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg
100 105 110
Asp Val Leu Arg Val Gly Ser Gly Gly Phe Trp Pro Arg Arg Ser Arg
115 120 125
Leu Trp Gly Gly Val Asp His Ala Pro Ala Gly Phe Asn Pro Thr Val

130	135	140
Thr Val Phe His Val Tyr Asp Ile Leu Glu Asn Val Glu His Ala Tyr 145 150 155 160		
Gly Met Arg Ala Ala Gln Phe His Ala Arg Phe Met Asp Ala Ile Thr 165 170 175		
Pro Thr Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly His 180 185 190		
Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met Asn 195 200 205		
Lys Glu Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp Leu 210 215 220		
Cys Glu Arg Met Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser Phe 225 230 235 240		
Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg Thr 245 250 255		
Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Ala Leu Phe Tyr Arg Val Tyr 260 265 270		
Val Arg Ser Gly Arg Val Leu Ser Tyr Leu Cys Asp Asn Phe Cys Pro 275 280 285		
Ala Ile Lys Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe Ile 290 295 300		
Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys Pro 305 310 315 320		
Gly Arg Asn Asn Thr Leu Ala Gln Pro Arg Ala Pro Met Ala Phe Gly 325 330 335		
Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala Ile 340 345 350		
Glu Gly Gly Met Ser Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe Asp 355 360 365		
Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val Ala 370 375 380		
Gly His Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr Asp 385 390 395 400		
Leu Ser Thr Thr Ala Leu Glu His Val Leu Leu Phe Ser Leu Gly Ser 405 410 415		
Cys Asp Leu Pro Glu Ser His Leu Asn Glu Leu Ala Ala Arg Gly Leu 420 425 430		
Pro Thr Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu Leu 435 440 445		
Ala Phe Met Thr Leu Val Lys Gln Tyr Gly Pro Glu Phe Val Thr Gly 450 455 460		

Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Leu Leu Ala Lys Leu Thr
 465 470 475 480
 Asp Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly Arg
 485 490 495
 Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys Arg
 500 505 510
 Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly Ile
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 Ile Thr Asp Lys Ile Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val Ala
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 Pro Ala Tyr Tyr Ala Ala Gly Pro Ala Gln Arg Gly Val Ile Gly Glu
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 Tyr Cys Ile Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys Phe
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 Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile Asn
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 Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr Cys
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 Leu Leu Arg Leu Ala Asp Gln Lys Gly Phe Ile Leu Pro Asp Thr Gln
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 Gly Arg Phe Arg Gly Ala Gly Gly Glu Ala Pro Lys Arg Pro Ala Ala
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 675 680 685
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 Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu Cys Phe Ser Thr Leu
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 Ser Leu Arg Ala Asp Ala Val Ala His Leu Glu Ala Gly Lys Asp Tyr
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 Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe Phe Val Lys Ala His
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 Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Ser Pro Glu Glu Ala
 785 790 795 800

Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val Cys Asn Ser
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 Arg Glu Tyr Val His Ala Arg Trp Ala Ala Phe Glu Gln Leu Leu Ala
 850 855 860
 Asp Phe Pro Glu Ala Ala Asp Met Arg Ala Pro Gly Pro Tyr Ser Met
 865 870 875 880
 Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu Cys Arg Gly
 885 890 895
 Leu Thr Ala Ala Gly Leu Thr Ala Met Gly Asp Lys Met Ala Ser His
 900 905 910
 Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys Leu Glu Cys Glu Lys
 915 920 925
 Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys Lys Tyr Ile Gly Val
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<213> herpes simplex

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Cys	Asp	Leu	Pro	Glu	Ser	His	Leu	Asn	Glu	Leu	Ala	Ala	Arg	Gly	Leu
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Met Phe Ser Gly Gly Gly Gly Pro Leu Ser Pro Gly Gly Lys Ser Ala
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 Ala Arg Ala Ala Ser Gly Phe Phe Ala Pro Ala Gly Pro Arg Gly Ala
 20 25 30
 Gly Arg Gly Pro Pro Pro Cys Leu Arg Gln Asn Phe Tyr Asn Pro Tyr
 35 40 45
 Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg
 50 55 60
 His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg
 65 70 75 80
 Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp
 85 90 95
 Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg

100					105					110					
Asp	Val	Leu	Arg	Val	Gly	Ser	Gly	Gly	Phe	Trp	Pro	Arg	Arg	Ser	Arg
	115						120					125			
Leu	Trp	Gly	Gly	Val	Asp	His	Ala	Pro	Ala	Gly	Phe	Asn	Pro	Thr	Val
	130					135					140				
Thr	Val	Phe	His	Val	Tyr	Asp	Ile	Leu	Glu	Asn	Val	Glu	His	Ala	Tyr
	145				150					155					160
Gly	Met	Arg	Ala	Ala	Gln	Phe	His	Ala	Arg	Phe	Met	Asp	Ala	Ile	Thr
			165						170					175	
Pro	Thr	Gly	Thr	Val	Ile	Thr	Leu	Leu	Gly	Leu	Thr	Pro	Glu	Gly	His
			180					185					190		
Arg	Val	Ala	Val	His	Val	Tyr	Gly	Thr	Arg	Gln	Tyr	Phe	Tyr	Met	Asn
	195						200					205			
Lys	Glu	Glu	Val	Asp	Arg	His	Leu	Gln	Cys	Arg	Ala	Pro	Arg	Asp	Leu
	210					215					220				
Cys	Glu	Arg	Met	Ala	Ala	Ala	Leu	Arg	Glu	Ser	Pro	Gly	Ala	Ser	Phe
	225				230					235					240
Arg	Gly	Ile	Ser	Ala	Asp	His	Phe	Glu	Ala	Glu	Val	Val	Glu	Arg	Thr
				245					250					255	
Asp	Val	Tyr	Tyr	Tyr	Glu	Thr	Arg	Pro	Ala	Leu	Phe	Tyr	Arg	Val	Tyr
		260						265					270		
Val	Arg	Ser	Gly	Arg	Val	Leu	Ser	Tyr	Leu	Cys	Asp	Asn	Phe	Cys	Pro
		275					280					285			
Ala	Ile	Lys	Lys	Tyr	Glu	Gly	Gly	Val	Asp	Ala	Thr	Thr	Arg	Phe	Ile
	290					295					300				
Leu	Asp	Asn	Pro	Gly	Phe	Val	Thr	Phe	Gly	Trp	Tyr	Arg	Leu	Lys	Pro
	305				310					315					320
Gly	Arg	Asn	Asn	Thr	Leu	Ala	Gln	Pro	Arg	Ala	Pro	Met	Ala	Phe	Gly
				325					330					335	
Thr	Ser	Ser	Asp	Val	Glu	Phe	Asn	Cys	Thr	Ala	Asp	Asn	Leu	Ala	Ile
			340					345					350		
Glu	Gly	Gly	Met	Ser	Asp	Leu	Pro	Ala	Tyr	Lys	Leu	Met	Cys	Phe	Asp
		355					360					365			
Ile	Glu	Cys	Lys	Ala	Gly	Gly	Glu	Asp	Glu	Leu	Ala	Phe	Pro	Val	Ala
	370					375					380				
Gly	His	Pro	Glu	Asp	Leu	Val	Ile	Gln	Ile	Ser	Cys	Leu	Leu	Tyr	Asp
	385				390					395					400
Leu	Ser	Thr	Thr	Ala	Leu	Glu	His	Val	Leu	Leu	Phe	Ser	Leu	Gly	Ser
				405					410					415	
Cys	Asp	Leu	Pro	Glu	Ser	His	Leu	Asn	Glu	Leu	Ala	Ala	Arg	Gly	Leu
			420					425					430		

Pro Thr Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu Leu
 435 440 445
 Ala Phe Met Thr Leu Val Lys Gln Tyr Gly Pro Glu Phe Val Thr Gly
 450 455 460
 Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Leu Leu Ala Lys Leu Thr
 465 470 475 480
 Asp Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly Arg
 485 490 495
 Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys Arg
 500 505 510
 Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly Ile
 515 520 525
 Ile Thr Asp Lys Ile Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val Ala
 530 535 540
 Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp Ile
 545 550 555 560
 Pro Thr Tyr Tyr Ala Ala Gly Pro Ala Gln Arg Gly Val Ile Gly Glu
 565 570 575
 Tyr Cys Ile Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys Phe
 580 585 590
 Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile Asn
 595 600 605
 Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr Cys
 610 615 620
 Leu Leu Arg Leu Ala Asp Gln Lys Gly Phe Ile Leu Pro Asp Thr Gln
 625 630 635 640
 Gly Arg Phe Arg Gly Ala Gly Gly Glu Ala Pro Lys Arg Pro Ala Ala
 645 650 655
 Ala Arg Glu Asp Glu Glu Arg Pro Glu Glu Glu Gly Glu Asp Glu Asn
 660 665 670
 Glu Arg Glu Glu Gly Gly Gly Glu Arg Glu Pro Glu Gly Ala Arg Glu
 675 680 685
 Thr Ala Gly Arg His Val Gly Tyr Gln Gly Ala Arg Val Leu Asp Pro
 690 695 700
 Thr Ser Gly Phe His Val Asn Pro Val Val Val Phe Asp Phe Ala Ser
 705 710 715 720
 Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu Cys Phe Ser Thr Leu
 725 730 735
 Ser Leu Arg Ala Asp Ala Val Ala His Leu Glu Ala Gly Lys Asp Tyr
 740 745 750
 Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe Phe Val Lys Ala His
 755 760 765

Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg Asp Trp Leu Ala Met
 770 775 780
 Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Ser Pro Glu Glu Ala
 785 790 795 800
 Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val Cys Asn Ser
 805 810 815
 Val Tyr Gly Phe Thr Gly Ala Gln His Gly Leu Leu Pro Cys Leu His
 820 825 830
 Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu Met Leu Leu Ala Thr
 835 840 845
 Arg Glu Tyr Val His Ala Arg Trp Ala Ala Phe Glu Gln Leu Leu Ala
 850 855 860
 Asp Phe Pro Glu Ala Ala Asp Met Arg Ala Pro Gly Pro Tyr Ser Met
 865 870 875 880
 Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu Cys Arg Gly
 885 890 895
 Leu Thr Ala Ala Gly Leu Thr Ala Val Gly Asp Lys Met Ala Ser His
 900 905 910
 Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys Leu Glu Cys Glu Lys
 915 920 925
 Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys Lys Tyr Ile Gly Val
 930 935 940
 Ile Tyr Gly Gly Lys Met Leu Ile Lys Gly Val Asp Leu Val Arg Lys
 945 950 955 960
 Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg Ala Leu Val Asp Leu
 965 970 975
 Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala Ala Ala Leu Ala Glu
 980 985 990
 Arg Pro Ala Glu Glu Trp Leu Ala Arg Pro Leu Pro Glu Gly Leu Gln
 995 1000 1005
 Ala Phe Gly Ala Val Leu Val Asp Ala His Arg Arg Ile Thr Asp
 1010 1015 1020
 Pro Glu Arg Asp Ile Gln Asp Phe Val Leu Thr Ala Glu Leu Ser
 1025 1030 1035
 Arg His Pro Arg Ala Tyr Thr Asn Lys Arg Leu Ala His Leu Thr
 1040 1045 1050
 Val Tyr Tyr Lys Leu Met Ala Arg Arg Ala Gln Val Pro Ser Ile
 1055 1060 1065
 Lys Asp Arg Ile Pro Tyr Val Ile Val Ala Gln Thr Arg Glu Val
 1070 1075 1080
 Glu Glu Thr Val Ala Arg Leu Ala Ala Leu Arg Glu Leu Asp Ala

1085	1090	1095
Ala Ala Pro Gly Asp Glu Pro	Ala Pro Pro Ala Ala	Leu Pro Ser
1100	1105	1110
Pro Ala Lys Arg Pro Arg Glu	Thr Pro Ser Pro Ala	Asp Pro Pro
1115	1120	1125
Gly Gly Ala Ser Lys Pro Arg	Lys Leu Leu Val Ser	Glu Leu Ala
1130	1135	1140
Glu Asp Pro Ala Tyr Ala Ile	Ala His Gly Val Ala	Leu Asn Thr
1145	1150	1155
Asp Tyr Tyr Phe Ser His Leu	Leu Gly Ala Ala Cys	Val Thr Phe
1160	1165	1170
Lys Ala Leu Phe Gly Asn Asn	Ala Lys Ile Thr Glu	Ser Leu Leu
1175	1180	1185
Lys Arg Phe Ile Pro Glu Val	Trp His Pro Pro Asp	Asp Val Ala
1190	1195	1200
Ala Arg Leu Arg Thr Ala Gly	Phe Gly Ala Val Gly	Ala Gly Ala
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Thr Ala Glu Glu Thr Arg Arg	Met Leu His Arg Ala	Phe Asp Thr
1220	1225	1230

Leu Ala
1235

<210> 11
<211> 3729
<212> DNA
<213> herpes simplex

<400> 11
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tttttgcaga tcgtgccgag aggtgtcatg ttcgacggtc agacgggggtt gatcaagcat 180
aagacgggac ggctgcctct catgttctat cgagagatta aacatttggtt gagtcatgac 240
atggtttggc cgtgtccttg gcgcgagacc ctgggtgggtc gcgtgggtggg acctattcgt 300
tttcacacct acgatcagac ggacgccgtg ctcttcttcg actcgccga aaacgtgtcg 360
ccgcgctatc gtcagcatct ggtgccttcg gggaacgtgt tgcgtttctt cggggccaca 420
gaacacggct acagtatctg cgtcaacgtt ttccgggcagc gcagctactt ttactgtgag 480
tacagcgaca ccgataggct gcgtgaggtc attgccagcg tgggcgaact agtgcccgaa 540
ccgcggacgc catacgcgt gtctgtcacg ccggccacca agacctccat ctatgggtac 600
gggacgcgac ccgtgcccga tttgcagtgt gtgtctatca gcaactggac catggccaga 660
aaaatcggcg agtatctgct ggagcagggt tttcccgtgt acgaggtccg tgtggatccg 720

ctgacgcggtt tggatcatcga tcggcgggac accacggttcg gctgggtgctc cgtgaatcgt	780
tacgactggc ggcagcaggg tcgcgcgtcg acttggtgata tcgaggtaga ctgcgatgctc	840
tctgacctgg tggctgtgcc cgacgacagc tcgtggccgc gctatcgatg cctgtccttc	900
gatatcgagt gcatgagcgg cgagggtggg tttccctgcg ccgagaagtc cgatgacatt	960
gtcattcaga tctcgtgcgt gtgctacgag acggggggaa acaccgccgt ggatcagggg	1020
atcccaaacg ggaacgatgg tcggggctgc acttcggagg gtgtgatctt tgggcactcg	1080
ggctctcatc tctttacgat cggcacctgc gggcaggtgg gccagacgt ggacgtctac	1140
gagttccctt ccgaatacga gctgctgctg ggctttatgc ttttctttca acggtacgcg	1200
ccggcctttg tgaccgggta caacatcaac tcttttgact tgaagtacat cctcacgcgt	1260
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ggccgctttt ttttacacag ccccgccgtg ggttttaagc ggcagtacgc cgccgctttt	1380
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tcggtggtta tcgacatgta ccctgtatgc atggccaaga ctaactcgcc caactataag	1500
ctcaactacta tggccgagct ttacctgcgg caacgcaagg atgacctgtc ttacaaggac	1560
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tcgccgccct tgcaatctgc gccgtccagt caggacggcg tttcacccgg ctccggcagt	1980
aacagtagta gcagcgtcg cgttttcagc gtcggctccg gcagtagtgg cggcgtcggc	2040
gtttccaacg acaatcacgg ccggggcgg actgcggcg tttcgtacca gggcgccacg	2100
gtgtttgagc ccgaggtggg ttactacaac gaccccgtag ccgtgttcga ctttgccagc	2160
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caccgctttg tgcgtgcttc ggtgcgcgtc tcggtgctct cggaactgct caacaagtgg	2340
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atgctgctcg acaaggaaca gatggcgctc aaagtaacgt gcaacgcttt ctacggtttt	2460
accggcgcg tgaacgggat gatgccgtgt ctgccatcg ccgccagcat cagcgcatc	2520
ggtcgcgaca tgctagagcg caggcgcggt tcatcaaag acaacttttc agagccgtgt	2580

tttttgcaca atttttttaa tcaggaagac tatgtagtgg gaacgcggga gggggattcg 2640
 gaggagagca gcgcgttacc ggaggggctc gaaacatcgt cagggggctc gaacgaacgg 2700
 cgggtggagg cgcgggtcat ctacggggac acggacagcg tgtttgtccg ctttcgtggc 2760
 ctgacgccgc aggtcttggg ggcgcgtggg cccagcctgg cgcactacgt gacggcctgt 2820
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 ctgctctttg aggatcgga ggtctcggaa gcagccgtgc gcctgtcgcg cctctcactc 3060
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 gtgctctcta aggacatctc gctgtaccgt caatctaacc tgccgcacat tgccgtcatt 3240
 aagcgattgg cggcccgttc tgaggagcta cctcgggtcg gggatcgggt cttttacgtt 3300
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 ctgtcggccc tctttcccg cggcgaaacc gcgcgcaagg acaagtttt gcacatgggtg 3660
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 tgctgttga 3729

<210> 12
 <211> 1242
 <212> PRT
 <213> herpes simplex

<400> 12

Met Phe Phe Asn Pro Tyr Leu Ser Gly Gly Val Thr Gly Gly Ala Val
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 Ala Gly Gly Arg Arg Gln Arg Ser Gln Pro Gly Ser Ala Gln Gly Ser
 20 25 30
 Gly Lys Arg Pro Pro Gln Lys Gln Phe Leu Gln Ile Val Pro Arg Gly
 35 40 45
 Val Met Phe Asp Gly Gln Thr Gly Leu Ile Lys His Lys Thr Gly Arg
 50 55 60
 Leu Pro Leu Met Phe Tyr Arg Glu Ile Lys His Leu Leu Ser His Asp
 65 70 75 80

Met Val Trp Pro Cys Pro Trp Arg Glu Thr Leu Val Gly Arg Val Val
 85 90 95
 Gly Pro Ile Arg Phe His Thr Tyr Asp Gln Thr Asp Ala Val Leu Phe
 100 105 110
 Phe Asp Ser Pro Glu Asn Val Ser Pro Arg Tyr Arg Gln His Leu Val
 115 120 125
 Pro Ser Gly Asn Val Leu Arg Phe Phe Gly Ala Thr Glu His Gly Tyr
 130 135 140
 Ser Ile Cys Val Asn Val Phe Gly Gln Arg Ser Tyr Phe Tyr Cys Glu
 145 150 155 160
 Tyr Ser Asp Thr Asp Arg Leu Arg Glu Val Ile Ala Ser Val Gly Glu
 165 170 175
 Leu Val Pro Glu Pro Arg Thr Pro Tyr Ala Val Ser Val Thr Pro Ala
 180 185 190
 Thr Lys Thr Ser Ile Tyr Gly Tyr Gly Thr Arg Pro Val Pro Asp Leu
 195 200 205
 Gln Cys Val Ser Ile Ser Asn Trp Thr Met Ala Arg Lys Ile Gly Glu
 210 215 220
 Tyr Leu Leu Glu Gln Gly Phe Pro Val Tyr Glu Val Arg Val Asp Pro
 225 230 235 240
 Leu Thr Arg Leu Val Ile Asp Arg Arg Ile Thr Thr Phe Gly Trp Cys
 245 250 255
 Ser Val Asn Arg Tyr Asp Trp Arg Gln Gln Gly Arg Ala Ser Thr Cys
 260 265 270
 Asp Ile Glu Val Asp Cys Asp Val Ser Asp Leu Val Ala Val Pro Asp
 275 280 285
 Asp Ser Ser Trp Pro Arg Tyr Arg Cys Leu Ser Phe Asp Ile Glu Cys
 290 295 300
 Met Ser Gly Glu Gly Gly Phe Pro Cys Ala Glu Lys Ser Asp Asp Ile
 305 310 315 320
 Val Ile Gln Ile Ser Cys Val Cys Tyr Glu Thr Gly Gly Asn Thr Ala
 325 330 335
 Val Asp Gln Gly Ile Pro Asn Gly Asn Asp Gly Arg Gly Cys Thr Ser
 340 345 350
 Glu Gly Val Ile Phe Gly His Ser Gly Leu His Leu Phe Thr Ile Gly
 355 360 365
 Thr Cys Gly Gln Val Gly Pro Asp Val Asp Val Tyr Glu Phe Pro Ser
 370 375 380
 Glu Tyr Glu Leu Leu Leu Gly Phe Met Leu Phe Phe Gln Arg Tyr Ala
 385 390 395 400
 Pro Ala Phe Val Thr Gly Tyr Asn Ile Asn Ser Phe Asp Leu Lys Tyr

405	410	415
Ile Leu Thr Arg Leu Glu Tyr Leu Tyr Lys Val Asp Ser Gln Arg Phe 420 425 430		
Cys Lys Leu Pro Thr Ala Gln Gly Gly Arg Phe Phe Leu His Ser Pro 435 440 445		
Ala Val Gly Phe Lys Arg Gln Tyr Ala Ala Ala Phe Pro Ser Ala Ser 450 455 460		
His Asn Asn Pro Ala Ser Thr Ala Ala Thr Lys Val Tyr Ile Ala Gly 465 470 475 480		
Ser Val Val Ile Asp Met Tyr Pro Val Cys Met Ala Lys Thr Asn Ser 485 490 495		
Pro Asn Tyr Lys Leu Asn Thr Met Ala Glu Leu Tyr Leu Arg Gln Arg 500 505 510		
Lys Asp Asp Leu Ser Tyr Lys Asp Ile Pro Arg Cys Phe Val Ala Asn 515 520 525		
Ala Glu Gly Arg Ala Gln Val Gly Arg Tyr Cys Leu Gln Asp Ala Val 530 535 540		
Leu Val Arg Asp Leu Phe Asn Thr Ile Asn Phe His Tyr Glu Ala Gly 545 550 555 560		
Ala Ile Ala Arg Leu Ala Lys Ile Pro Leu Arg Arg Val Ile Phe Asp 565 570 575		
Gly Gln Gln Ile Arg Ile Tyr Thr Ser Leu Leu Asp Glu Cys Ala Cys 580 585 590		
Arg Asp Phe Ile Leu Pro Asn His Tyr Ser Lys Gly Thr Thr Val Pro 595 600 605		
Glu Thr Asn Ser Val Ala Val Ser Pro Asn Ala Ala Ile Ile Ser Thr 610 615 620		
Ala Ala Val Pro Gly Asp Ala Gly Ser Val Ala Ala Met Phe Gln Met 625 630 635 640		
Ser Pro Pro Leu Gln Ser Ala Pro Ser Ser Gln Asp Gly Val Ser Pro 645 650 655		
Gly Ser Gly Ser Asn Ser Ser Ser Ser Val Gly Val Phe Ser Val Gly 660 665 670		
Ser Gly Ser Ser Gly Gly Val Gly Val Ser Asn Asp Asn His Gly Ala 675 680 685		
Gly Gly Thr Ala Ala Val Ser Tyr Gln Gly Ala Thr Val Phe Glu Pro 690 695 700		
Glu Val Gly Tyr Tyr Asn Asp Pro Val Ala Val Phe Asp Phe Ala Ser 705 710 715 720		
Leu Tyr Pro Ser Ile Ile Met Ala His Asn Leu Cys Tyr Ser Thr Leu 725 730 735		

Leu Val Pro Gly Gly Glu Tyr Pro Val Asp Pro Ala Asp Val Tyr Ser
 740 745 750
 Val Thr Leu Glu Asn Gly Val Thr His Arg Phe Val Arg Ala Ser Val
 755 760 765
 Arg Val Ser Val Leu Ser Glu Leu Leu Asn Lys Trp Val Ser Gln Arg
 770 775 780
 Arg Ala Val Arg Glu Cys Met Arg Glu Cys Gln Asp Pro Val Arg Arg
 785 790 795 800
 Met Leu Leu Asp Lys Glu Gln Met Ala Leu Lys Val Thr Cys Asn Ala
 805 810 815
 Phe Tyr Gly Phe Thr Gly Ala Leu Asn Gly Met Met Pro Cys Leu Pro
 820 825 830
 Ile Ala Ala Ser Ile Thr Arg Ile Gly Arg Asp Met Leu Glu Arg Thr
 835 840 845
 Ala Arg Phe Ile Lys Asp Asn Phe Ser Glu Pro Cys Phe Leu His Asn
 850 855 860
 Phe Phe Asn Gln Glu Asp Tyr Val Val Gly Thr Arg Glu Gly Asp Ser
 865 870 875 880
 Glu Glu Ser Ser Ala Leu Pro Glu Gly Leu Glu Thr Ser Ser Gly Gly
 885 890 895
 Ser Asn Glu Arg Arg Val Glu Ala Arg Val Ile Tyr Gly Asp Thr Asp
 900 905 910
 Ser Val Phe Val Arg Phe Arg Gly Leu Thr Pro Gln Ala Leu Val Ala
 915 920 925
 Arg Gly Pro Ser Leu Ala His Tyr Val Thr Ala Cys Leu Phe Val Glu
 930 935 940
 Pro Val Lys Leu Glu Phe Glu Lys Val Phe Val Ser Leu Met Met Ile
 945 950 955 960
 Cys Lys Lys Arg Tyr Ile Gly Lys Val Glu Gly Ala Ser Gly Leu Ser
 965 970 975
 Met Lys Gly Val Asp Leu Val Arg Lys Thr Ala Cys Glu Phe Val Lys
 980 985 990
 Gly Val Thr Arg Asp Val Leu Ser Leu Leu Phe Glu Asp Arg Glu Val
 995 1000 1005
 Ser Glu Ala Ala Val Arg Leu Ser Arg Leu Ser Leu Asp Glu Val
 1010 1015 1020
 Lys Lys Tyr Gly Val Pro Arg Gly Phe Trp Arg Ile Leu Arg Arg
 1025 1030 1035
 Leu Val Gln Ala Arg Asp Asp Leu Tyr Leu His Arg Val Arg Val
 1040 1045 1050
 Glu Asp Leu Val Leu Ser Ser Val Leu Ser Lys Asp Ile Ser Leu
 1055 1060 1065

Tyr Arg Gln Ser Asn Leu Pro His Ile Ala Val Ile Lys Arg Leu
 1070 1075 1080
 Ala Ala Arg Ser Glu Glu Leu Pro Ser Val Gly Asp Arg Val Phe
 1085 1090 1095
 Tyr Val Leu Thr Ala Pro Gly Val Arg Thr Ala Pro Gln Gly Ser
 1100 1105 1110
 Ser Asp Asn Gly Asp Ser Val Thr Ala Gly Val Val Ser Arg Ser
 1115 1120 1125
 Asp Ala Ile Asp Gly Thr Asp Asp Asp Ala Asp Gly Gly Gly Val
 1130 1135 1140
 Glu Glu Ser Asn Arg Arg Gly Gly Glu Pro Ala Lys Lys Arg Ala
 1145 1150 1155
 Arg Lys Pro Pro Ser Ala Val Cys Asn Tyr Glu Val Ala Glu Asp
 1160 1165 1170
 Pro Ser Tyr Val Arg Glu His Gly Val Pro Ile His Ala Asp Lys
 1175 1180 1185
 Tyr Phe Glu Gln Val Leu Lys Ala Val Thr Asn Val Leu Ser Pro
 1190 1195 1200
 Val Phe Pro Gly Gly Glu Thr Ala Arg Lys Asp Lys Phe Leu His
 1205 1210 1215
 Met Val Leu Pro Arg Arg Leu His Leu Glu Pro Ala Phe Leu Pro
 1220 1225 1230
 Tyr Ser Val Lys Ala His Glu Cys Cys
 1235 1240

<210> 13
 <211> 1242
 <212> PRT
 <213> herpes simplex

<400> 13

Met Phe Phe Asn Pro Tyr Leu Ser Gly Gly Val Thr Gly Gly Ala Val
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 Ala Gly Gly Arg Arg Gln Arg Ser Gln Pro Gly Ser Ala Gln Gly Ser
 20 25 30
 Gly Lys Arg Pro Pro Gln Lys Gln Phe Leu Gln Ile Val Pro Arg Gly
 35 40 45
 Val Met Phe Asp Gly Gln Thr Gly Leu Ile Lys His Lys Thr Gly Arg
 50 55 60
 Leu Pro Leu Met Phe Tyr Arg Glu Ile Lys His Leu Leu Ser His Asp
 65 70 75 80
 Met Val Trp Pro Cys Pro Trp Arg Glu Thr Leu Val Gly Arg Val Val
 85 90 95

Gly Pro Ile Arg Phe His Thr Tyr Asp Gln Thr Asp Ala Val Leu Phe
 100 105 110
 Phe Asp Ser Pro Glu Asn Val Ser Pro Arg Tyr Arg Gln His Leu Val
 115 120 125
 Pro Ser Gly Asn Val Leu Arg Phe Phe Gly Ala Thr Glu His Gly Tyr
 130 135 140
 Ser Ile Cys Val Asn Val Phe Gly Gln Arg Ser Tyr Phe Tyr Cys Glu
 145 150 155 160
 Tyr Ser Asp Thr Asp Arg Leu Arg Glu Val Ile Ala Ser Val Gly Glu
 165 170 175
 Leu Val Pro Glu Pro Arg Thr Pro Tyr Ala Val Ser Val Thr Pro Ala
 180 185 190
 Thr Lys Thr Ser Ile Tyr Gly Tyr Gly Thr Arg Pro Val Pro Asp Leu
 195 200 205
 Gln Cys Val Ser Ile Ser Asn Trp Thr Met Ala Arg Lys Ile Gly Glu
 210 215 220
 Tyr Leu Leu Glu Gln Gly Phe Pro Val Tyr Glu Val Arg Val Asp Pro
 225 230 235 240
 Leu Thr Arg Leu Val Ile Asp Arg Arg Ile Thr Thr Phe Gly Trp Cys
 245 250 255
 Ser Val Asn Arg Tyr Asp Trp Arg Gln Gln Gly Arg Ala Ser Thr Cys
 260 265 270
 Asp Ile Glu Val Asp Cys Asp Val Ser Asp Leu Val Ala Val Pro Asp
 275 280 285
 Asp Ser Ser Trp Pro Arg Tyr Arg Cys Leu Ser Phe Asp Ile Glu Cys
 290 295 300
 Met Ser Gly Glu Gly Gly Phe Pro Cys Ala Glu Lys Ser Asp Asp Ile
 305 310 315 320
 Val Ile Gln Ile Ser Cys Val Cys Tyr Glu Thr Gly Gly Asn Thr Ala
 325 330 335
 Val Asp Gln Gly Ile Pro Asn Gly Asn Asp Gly Arg Gly Cys Thr Ser
 340 345 350
 Glu Gly Val Ile Phe Gly His Ser Gly Leu His Leu Phe Thr Ile Gly
 355 360 365
 Thr Cys Gly Gln Val Gly Pro Asp Val Asp Val Tyr Glu Phe Pro Ser
 370 375 380
 Glu Tyr Glu Leu Leu Leu Gly Phe Met Leu Phe Phe Gln Arg Tyr Ala
 385 390 395 400
 Pro Ala Phe Val Thr Gly Tyr Asn Ile Asn Ser Phe Asp Leu Lys Tyr
 405 410 415
 Ile Leu Thr Arg Leu Glu Tyr Leu Tyr Lys Val Asp Ser Gln Arg Phe
 420 425 430

Cys Lys Leu Pro Thr Ala Gln Gly Gly Arg Phe Phe Leu His Ser Pro
 435 440 445
 Ala Val Gly Phe Lys Arg Gln Tyr Ala Ala Ala Phe Pro Ser Ala Ser
 450 455 460
 His Asn Asn Pro Ala Ser Thr Ala Ala Thr Lys Val Tyr Ile Ala Gly
 465 470 475 480
 Ser Val Val Ile Asp Met Tyr Pro Val Cys Met Ala Lys Thr Asn Ser
 485 490 495
 Pro Asn Tyr Lys Leu Asn Thr Met Ala Glu Leu Tyr Leu Arg Gln Arg
 500 505 510
 Lys Asp Asp Leu Ser Tyr Lys Asp Ile Pro Arg Cys Phe Val Ala Asn
 515 520 525
 Ala Glu Gly Arg Ala Gln Val Gly Arg Tyr Cys Leu Gln Asp Ala Val
 530 535 540
 Leu Val Arg Asp Leu Phe Asn Thr Ile Asn Phe His Tyr Glu Ala Gly
 545 550 555 560
 Ala Ile Ala Arg Leu Ala Lys Ile Pro Leu Arg Arg Val Ile Phe Asp
 565 570 575
 Gly Gln Gln Ile Arg Ile Tyr Thr Ser Leu Leu Asp Glu Cys Ala Cys
 580 585 590
 Arg Asp Phe Ile Leu Pro Asn His Tyr Ser Lys Gly Thr Thr Val Pro
 595 600 605
 Glu Thr Asn Ser Val Ala Val Ser Pro Asn Ala Ala Ile Ile Ser Thr
 610 615 620
 Ala Ala Val Pro Gly Asp Ala Gly Ser Val Ala Ala Met Phe Gln Met
 625 630 635 640
 Ser Pro Pro Leu Gln Ser Ala Pro Ser Ser Gln Asp Gly Val Ser Pro
 645 650 655
 Gly Ser Gly Ser Asn Ser Ser Ser Ser Val Gly Val Phe Ser Val Gly
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 Ser Gly Ser Ser Gly Gly Val Gly Val Ser Asn Asp Asn His Gly Ala
 675 680 685
 Gly Gly Thr Ala Ala Val Ser Tyr Gln Gly Ala Thr Val Phe Glu Pro
 690 695 700
 Glu Val Gly Tyr Tyr Asn Asp Pro Val Ala Val Phe Asp Phe Ala Ser
 705 710 715 720
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 725 730 735
 Leu Val Pro Gly Gly Glu Tyr Pro Val Asp Pro Ala Asp Val Tyr Ser
 740 745 750
 Val Thr Leu Glu Asn Gly Val Thr His Arg Phe Val Arg Ala Ser Val

755					760					765					
Arg	Val	Ser	Val	Leu	Ser	Glu	Leu	Leu	Asn	Lys	Trp	Val	Ser	Gln	Arg
770					775					780					
Arg	Ala	Val	Arg	Glu	Cys	Met	Arg	Glu	Cys	Gln	Asp	Pro	Val	Arg	Arg
785					790					795					800
Met	Leu	Leu	Asp	Lys	Glu	Gln	Met	Ala	Leu	Lys	Val	Thr	Cys	Asn	Ala
				805					810					815	
Phe	Tyr	Gly	Phe	Thr	Gly	Val	Val	Asn	Gly	Met	Met	Pro	Cys	Leu	Pro
			820					825						830	
Ile	Ala	Ala	Ser	Ile	Thr	Arg	Ile	Gly	Arg	Asp	Met	Leu	Glu	Arg	Thr
			835					840						845	
Ala	Arg	Phe	Ile	Lys	Asp	Asn	Phe	Ser	Glu	Pro	Cys	Phe	Leu	His	Asn
				850					855					860	
Phe	Phe	Asn	Gln	Glu	Asp	Tyr	Val	Val	Gly	Thr	Arg	Glu	Gly	Asp	Ser
865									870					875	880
Glu	Glu	Ser	Ser	Ala	Leu	Pro	Glu	Gly	Leu	Glu	Thr	Ser	Ser	Gly	Gly
				885					890					895	
Ser	Asn	Glu	Arg	Arg	Val	Glu	Ala	Arg	Val	Ile	Tyr	Gly	Asp	Thr	Asp
			900					905						910	
Ser	Val	Phe	Val	Arg	Phe	Arg	Gly	Leu	Thr	Pro	Gln	Ala	Leu	Val	Ala
			915					920						925	
Arg	Gly	Pro	Ser	Leu	Ala	His	Tyr	Val	Thr	Ala	Cys	Leu	Phe	Val	Glu
				930					935					940	
Pro	Val	Lys	Leu	Glu	Phe	Glu	Lys	Val	Phe	Val	Ser	Leu	Met	Met	Ile
945									950					955	960
Cys	Lys	Lys	Arg	Tyr	Ile	Gly	Lys	Val	Glu	Gly	Ala	Ser	Gly	Leu	Ser
				965					970					975	
Met	Lys	Gly	Val	Asp	Leu	Val	Arg	Lys	Thr	Ala	Cys	Glu	Phe	Val	Lys
			980					985						990	
Gly	Val	Thr	Arg	Asp	Val	Leu	Ser	Leu	Leu	Phe	Glu	Asp	Arg	Glu	Val
			995					1000						1005	
Ser	Glu	Ala	Ala	Val	Arg	Leu	Ser	Arg	Leu	Ser	Leu	Asp	Glu	Val	
			1010					1015					1020		
Lys	Lys	Tyr	Gly	Val	Pro	Arg	Gly	Phe	Trp	Arg	Ile	Leu	Arg	Arg	
			1025					1030					1035		
Leu	Val	Gln	Ala	Arg	Asp	Asp	Leu	Tyr	Leu	His	Arg	Val	Arg	Val	
			1040					1045					1050		
Glu	Asp	Leu	Val	Leu	Ser	Ser	Val	Leu	Ser	Lys	Asp	Ile	Ser	Leu	
			1055					1060					1065		
Tyr	Arg	Gln	Ser	Asn	Leu	Pro	His	Ile	Ala	Val	Ile	Lys	Arg	Leu	
			1070					1075					1080		

Ala Ala Arg Ser Glu Glu Leu Pro Ser Val Gly Asp Arg Val Phe
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 Tyr Val Leu Thr Ala Pro Gly Val Arg Thr Ala Pro Gln Gly Ser
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 Ser Asp Asn Gly Asp Ser Val Thr Ala Gly Val Val Ser Arg Ser
 1115 1120 1125
 Asp Ala Ile Asp Gly Thr Asp Asp Asp Ala Asp Gly Gly Gly Val
 1130 1135 1140
 Glu Glu Ser Asn Arg Arg Gly Gly Glu Pro Ala Lys Lys Arg Ala
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 Arg Lys Pro Pro Ser Ala Val Cys Asn Tyr Glu Val Ala Glu Asp
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 Pro Ser Tyr Val Arg Glu His Gly Val Pro Ile His Ala Asp Lys
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 Tyr Phe Glu Gln Val Leu Lys Ala Val Thr Asn Val Leu Ser Pro
 1190 1195 1200
 Val Phe Pro Gly Gly Glu Thr Ala Arg Lys Asp Lys Phe Leu His
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 35 40 45
 His Leu Ala Gln Thr Gly Thr Gln Pro Lys Ala Pro Gly Pro Ala Gln
 50 55 60
 Arg His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro
 65 70 75 80
 Arg Ser Leu Asp Glu Asp Ala Pro Ala Glu Gln Arg Thr Gly Val His
 85 90 95
 Asp Gly Arg Leu Arg Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu
 100 105 110
 Arg Asp Val Leu Arg Val Gly Pro Glu Gly Phe Trp Pro Arg Arg Leu

115					120					125					
Arg	Leu	Trp	Gly	Gly	Ala	Asp	His	Ala	Pro	Lys	Gly	Phe	Asp	Pro	Thr
130						135					140				
Val	Thr	Val	Phe	His	Val	Tyr	Asp	Ile	Leu	Glu	His	Val	Glu	His	Ala
145					150					155					160
Tyr	Ser	Met	Arg	Ala	Ala	Gln	Leu	His	Glu	Arg	Phe	Met	Asp	Ala	Ile
				165					170					175	
Thr	Pro	Ala	Gly	Thr	Val	Ile	Thr	Leu	Leu	Gly	Leu	Thr	Pro	Glu	Gly
			180					185					190		
His	Arg	Val	Ala	Val	His	Val	Tyr	Gly	Thr	Arg	Gln	Tyr	Phe	Tyr	Met
		195					200					205			
Asn	Lys	Ala	Glu	Val	Asp	Arg	His	Leu	Gln	Cys	Arg	Ala	Pro	Arg	Asp
	210					215					220				
Leu	Cys	Glu	Arg	Leu	Ala	Ala	Ala	Leu	Arg	Glu	Ser	Pro	Gly	Ala	Ser
225					230					235					240
Phe	Arg	Gly	Ile	Ser	Ala	Asp	His	Phe	Glu	Ala	Glu	Val	Val	Glu	Arg
				245					250					255	
Ala	Asp	Val	Tyr	Tyr	Tyr	Glu	Thr	Arg	Pro	Thr	Leu	Tyr	Tyr	Arg	Val
		260						265					270		
Phe	Val	Arg	Ser	Gly	Arg	Ala	Leu	Ala	Tyr	Leu	Cys	Asp	Asn	Phe	Cys
		275					280					285			
Pro	Ala	Ile	Arg	Lys	Tyr	Glu	Gly	Gly	Val	Asp	Ala	Thr	Thr	Arg	Phe
	290					295					300				
Ile	Leu	Asp	Asn	Pro	Gly	Phe	Val	Thr	Phe	Gly	Trp	Tyr	Arg	Leu	Lys
305					310					315					320
Pro	Gly	Arg	Gly	Asn	Ala	Pro	Ala	Gln	Pro	Arg	Pro	Pro	Thr	Ala	Phe
				325					330					335	
Gly	Thr	Ser	Ser	Asp	Val	Glu	Phe	Asn	Cys	Thr	Ala	Asp	Asn	Leu	Ala
			340					345					350		
Val	Glu	Gly	Ala	Met	Cys	Asp	Leu	Pro	Ala	Tyr	Lys	Leu	Met	Cys	Phe
		355					360					365			
Asp	Ile	Glu	Cys	Lys	Ala	Gly	Gly	Glu	Asp	Glu	Leu	Ala	Phe	Pro	Val
	370					375					380				
Ala	Glu	Arg	Pro	Glu	Asp	Leu	Val	Ile	Gln	Ile	Ser	Cys	Leu	Leu	Tyr
385					390					395					400
Asp	Leu	Ser	Thr	Thr	Ala	Leu	Glu	His	Ile	Leu	Leu	Phe	Ser	Leu	Gly
				405					410					415	
Ser	Cys	Asp	Leu	Pro	Glu	Ser	His	Leu	Ser	Asp	Leu	Ala	Ser	Arg	Gly
			420					425					430		
Leu	Pro	Ala	Pro	Val	Val	Leu	Glu	Phe	Asp	Ser	Glu	Phe	Glu	Met	Leu
		435					440					445			

Leu Ala Phe Met Thr Phe Val Lys Gln Tyr Gly Pro Glu Phe Val Thr
 450 455 460
 Gly Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Val Leu Thr Lys Leu
 465 470 475 480
 Thr Glu Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly
 485 490 495
 Arg Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys
 500 505 510
 Arg Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly
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 Ile Ile Thr Asp Lys Val Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val
 530 535 540
 Ala Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp
 545 550 555 560
 Ile Pro Ala Tyr Tyr Ala Ser Gly Pro Ala Gln Arg Gly Val Ile Gly
 565 570 575
 Glu Tyr Cys Val Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys
 580 585 590
 Phe Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile
 595 600 605
 Asn Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr
 610 615 620
 Cys Leu Leu Arg Leu Ala Gly Gln Lys Gly Phe Ile Leu Pro Asp Thr
 625 630 635 640
 Gln Gly Arg Phe Arg Gly Leu Asp Lys Glu Ala Pro Lys Arg Pro Ala
 645 650 655
 Val Pro Arg Gly Glu Gly Glu Arg Pro Gly Asp Gly Asn Gly Asp Glu
 660 665 670
 Asp Lys Asp Asp Asp Glu Asp Glu Asp Gly Asp Glu Arg Glu Glu Val
 675 680 685
 Ala Arg Glu Thr Gly Gly Arg His Val Gly Tyr Gln Gly Ala Arg Val
 690 695 700
 Leu Asp Pro Thr Ser Gly Phe His Val Asp Pro Val Val Val Phe Asp
 705 710 715 720
 Phe Ala Ser Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu Cys Phe
 725 730 735
 Ser Thr Leu Ser Leu Arg Pro Glu Ala Val Ala His Leu Glu Ala Asp
 740 745 750
 Arg Asp Tyr Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe Phe Val
 755 760 765
 Lys Ala His Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg Asp Trp
 770 775 780

Leu Ala Met Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Thr Pro
 785 790 795 800
 Glu Glu Ala Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val
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 Cys Asn Ser Val Tyr Gly Phe Thr Gly Val Gln His Gly Leu Leu Pro
 820 825 830
 Cys Leu His Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu Met Leu
 835 840 845
 Leu Ala Thr Arg Ala Tyr Val His Ala Arg Trp Ala Glu Phe Asp Gln
 850 855 860
 Leu Leu Ala Asp Phe Pro Glu Ala Ala Gly Met Arg Ala Pro Gly Pro
 865 870 875 880
 Tyr Ser Met Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu
 885 890 895
 Cys Arg Gly Leu Thr Ala Ala Gly Leu Val Ala Met Gly Asp Lys Met
 900 905 910
 Ala Ser His Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys Leu Glu
 915 920 925
 Cys Glu Lys Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys Lys Tyr
 930 935 940
 Ile Gly Val Ile Cys Gly Gly Lys Met Leu Ile Lys Gly Val Asp Leu
 945 950 955 960
 Val Arg Lys Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg Ala Leu
 965 970 975
 Val Asp Leu Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala Ala Ala
 980 985 990
 Leu Ala Glu Arg Pro Ala Glu Glu Trp Leu Ala Arg Pro Leu Pro Glu
 995 1000 1005
 Gly Leu Gln Ala Phe Gly Ala Val Leu Val Asp Ala His Arg Arg
 1010 1015 1020
 Ile Thr Asp Pro Glu Arg Asp Ile Gln Asp Phe Val Leu Thr Ala
 1025 1030 1035
 Glu Leu Ser Arg His Pro Arg Ala Tyr Thr Asn Lys Arg Leu Ala
 1040 1045 1050
 His Leu Thr Val Tyr Tyr Lys Leu Met Ala Arg Arg Ala Gln Val
 1055 1060 1065
 Pro Ser Ile Lys Asp Arg Ile Pro Tyr Val Ile Val Ala Gln Thr
 1070 1075 1080
 Arg Glu Val Glu Glu Thr Val Ala Arg Leu Ala Ala Leu Arg Glu
 1085 1090 1095
 Leu Asp Ala Ala Ala Pro Gly Asp Glu Pro Ala Pro Pro Ala Ala

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Leu Pro Ser Pro Ala Lys Arg	Pro Arg Glu Thr Pro Ser His Ala	
1115	1120	1125
Asp Pro Pro Gly Gly Ala Ser	Lys Pro Arg Lys Leu Leu Val Ser	
1130	1135	1140
Glu Leu Ala Glu Asp Pro Gly	Tyr Ala Ile Ala Arg Gly Val Pro	
1145	1150	1155
Leu Asn Thr Asp Tyr Tyr Phe	Ser His Leu Leu Gly Ala Ala Cys	
1160	1165	1170
Val Thr Phe Lys Ala Leu Phe	Gly Asn Asn Ala Lys Ile Thr Glu	
1175	1180	1185
Ser Leu Leu Lys Arg Phe Ile	Pro Glu Thr Trp His Pro Pro Asp	
1190	1195	1200
Asp Val Ala Ala Arg Leu Arg	Ala Ala Gly Phe Gly Pro Ala Gly	
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Thr Gln Thr Ala Pro Pro Pro Cys Arg Arg Gln Asn Phe Tyr Asn Pro		
35 40 45		
His Leu Ala Gln Thr Gly Thr Gln Pro Lys Ala Pro Gly Pro Ala Gln		
50 55 60		
Arg His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro		
65 70 75 80		
Arg Ser Leu Asp Glu Asp Ala Pro Ala Glu Gln Arg Thr Gly Val His		
85 90 95		
Asp Gly Arg Leu Arg Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu		
100 105 110		
Arg Asp Val Leu Arg Val Gly Pro Glu Gly Phe Trp Pro Arg Arg Leu		
115 120 125		
Arg Leu Trp Gly Gly Ala Asp His Ala Pro Glu Gly Phe Asp Pro Thr		
130 135 140		

Val Thr Val Phe His Val Tyr Asp Ile Leu Glu His Val Glu His Ala
 145 150 155 160
 Tyr Ser Met Arg Ala Ala Gln Leu His Glu Arg Phe Met Asp Ala Ile
 165 170 175
 Thr Pro Ala Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly
 180 185 190
 His Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met
 195 200 205
 Asn Lys Ala Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp
 210 215 220
 Leu Cys Glu Arg Leu Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser
 225 230 235 240
 Phe Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg
 245 250 255
 Ala Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Thr Leu Tyr Tyr Arg Val
 260 265 270
 Phe Val Arg Ser Gly Arg Ala Leu Ala Tyr Leu Cys Asp Asn Phe Cys
 275 280 285
 Pro Ala Ile Arg Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe
 290 295 300
 Ile Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys
 305 310 315 320
 Pro Gly Arg Gly Asn Ala Pro Ala Gln Pro Arg Pro Pro Thr Ala Phe
 325 330 335
 Gly Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala
 340 345 350
 Val Glu Gly Ala Met Cys Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe
 355 360 365
 Asp Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val
 370 375 380
 Ala Glu Arg Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr
 385 390 395 400
 Asp Leu Ser Thr Thr Ala Leu Glu His Ile Leu Leu Phe Ser Leu Gly
 405 410 415
 Ser Cys Asp Leu Pro Glu Ser His Leu Ser Asp Leu Ala Ser Arg Gly
 420 425 430
 Leu Pro Ala Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu
 435 440 445
 Leu Ala Phe Met Thr Phe Val Lys Gln Tyr Gly Pro Glu Phe Val Thr
 450 455 460
 Gly Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Val Leu Thr Lys Leu

465	470	475	480
Thr Glu Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly			
	485	490	495
Arg Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys			
	500	505	510
Arg Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly			
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Ile Ile Thr Asp Lys Val Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val			
	530	535	540
Ala Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp			
	545	550	555
Ile Pro Ala Tyr Tyr Ala Ser Gly Pro Ala Gln Arg Gly Val Ile Gly			
	565	570	575
Glu Tyr Cys Val Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys			
	580	585	590
Phe Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile			
	595	600	605
Asn Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr			
	610	615	620
Cys Leu Leu Arg Leu Ala Gly Gln Lys Gly Phe Ile Leu Pro Asp Thr			
	625	630	635
Gln Gly Arg Phe Arg Gly Leu Asp Lys Glu Ala Pro Lys Arg Pro Ala			
	645	650	655
Val Pro Arg Gly Glu Gly Glu Arg Pro Gly Asp Gly Asn Gly Asp Glu			
	660	665	670
Asp Lys Asp Asp Asp Glu Asp Gly Asp Glu Asp Gly Asp Glu Arg Glu			
	675	680	685
Glu Val Ala Arg Glu Thr Gly Gly Arg His Val Gly Tyr Gln Gly Ala			
	690	695	700
Arg Val Leu Asp Pro Thr Ser Gly Phe His Val Asp Pro Val Val Val			
	705	710	715
Phe Asp Phe Ala Ser Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu			
	725	730	735
Cys Phe Ser Thr Leu Ser Leu Arg Pro Glu Ala Val Ala His Leu Glu			
	740	745	750
Ala Asp Arg Asp Tyr Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe			
	755	760	765
Phe Val Lys Ala His Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg			
	770	775	780
Asp Trp Leu Ala Met Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser			
	785	790	795
			800

Pro Pro Glu Glu Ala Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys
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 Val Val Cys Asn Ser Val Tyr Gly Phe Thr Gly Val Gln His Gly Leu
 820 825 830
 Leu Pro Cys Leu His Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu
 835 840 845
 Met Leu Leu Ala Thr Arg Ala Tyr Val His Ala Arg Trp Ala Glu Phe
 850 855 860
 Asp Gln Leu Leu Ala Asp Phe Pro Glu Ala Ala Gly Met Arg Ala Pro
 865 870 875 880
 Gly Pro Tyr Ser Met Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe
 885 890 895
 Val Leu Cys Arg Gly Leu Thr Ala Ala Gly Leu Val Ala Met Gly Asp
 900 905 910
 Lys Met Ala Ser His Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys
 915 920 925
 Leu Glu Cys Glu Lys Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys
 930 935 940
 Lys Tyr Ile Gly Val Ile Cys Gly Gly Lys Met Leu Ile Lys Gly Val
 945 950 955 960
 Asp Leu Val Arg Lys Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg
 965 970 975
 Ala Leu Val Asp Leu Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala
 980 985 990
 Ala Ala Leu Ala Glu Arg Pro Ala Glu Glu Trp Leu Ala Arg Pro Leu
 995 1000 1005
 Pro Glu Gly Leu Gln Ala Phe Gly Ala Val Leu Val Asp Ala His
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 Arg Arg Ile Thr Asp Pro Glu Arg Asp Ile Gln Asp Phe Val Leu
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 Thr Ala Glu Leu Ser Arg His Pro Arg Ala Tyr Thr Asn Lys Arg
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 Gln Val Pro Ser Ile Lys Asp Arg Ile Pro Tyr Val Ile Val Ala
 1070 1075 1080
 Gln Thr Arg Glu Val Glu Glu Thr Val Ala Arg Leu Ala Ala Leu
 1085 1090 1095
 Arg Glu Leu Asp Ala Ala Ala Pro Gly Asp Glu Pro Ala Pro Pro
 1100 1105 1110
 Ala Ala Leu Pro Ser Pro Ala Lys Arg Pro Arg Glu Thr Pro Ser
 1115 1120 1125

His Ala Asp Pro Pro Gly Gly Ala Ser Lys Pro Arg Lys Leu Leu
 1130 1135 1140

Val Ser Glu Leu Ala Glu Asp Pro Gly Tyr Ala Ile Ala Arg Gly
 1145 1150 1155

Val Pro Leu Asn Thr Asp Tyr Tyr Phe Ser His Leu Leu Gly Ala
 1160 1165 1170

Ala Cys Val Thr Phe Lys Ala Leu Phe Gly Asn Asn Ala Lys Ile
 1175 1180 1185

Thr Glu Ser Leu Leu Lys Arg Phe Ile Pro Glu Thr Trp His Pro
 1190 1195 1200

Pro Asp Asp Val Ala Ala Arg Leu Arg Ala Ala Gly Phe Gly Pro
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Ala Gly Ala Gly Ala Thr Ala Glu Glu Thr Arg Arg Met Leu His
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Arg Ala Phe Asp Thr Leu Ala
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Met Phe Ser Gly Gly Gly Gly Pro Leu Ser Pro Gly Gly Lys Ser Ala
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Gly Arg Gly Pro Pro Pro Cys Leu Arg Gln Asn Phe Tyr Asn Pro Tyr
 35 40 45

Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg
 50 55 60

His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg
 65 70 75 80

Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp
 85 90 95

Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg
 100 105 110

Asp Val Leu Arg Val Gly Ser Gly Gly Phe Trp Pro Arg Arg Ser Arg
 115 120 125

Leu Trp Gly Gly Val Asp His Ala Pro Ala Gly Phe Asn Pro Thr Val
 130 135 140

Thr Val Phe His Val Tyr Asp Ile Leu Glu Asn Val Glu His Ala Tyr
 145 150 155 160

Gly Met Arg Ala Ala Gln Phe His Ala Arg Phe Met Asp Ala Ile Thr
 165 170 175
 Pro Thr Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly His
 180 185 190
 Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met Asn
 195 200 205
 Lys Glu Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp Leu
 210 215 220
 Cys Glu Arg Met Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser Phe
 225 230 235 240
 Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg Thr
 245 250 255
 Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Ala Leu Phe Tyr Arg Val Tyr
 260 265 270
 Val Arg Ser Gly Arg Val Leu Ser Tyr Leu Cys Asp Asn Phe Cys Pro
 275 280 285
 Ala Ile Lys Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe Ile
 290 295 300
 Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys Pro
 305 310 315 320
 Gly Arg Asn Asn Thr Leu Ala Gln Pro Arg Ala Pro Met Ala Phe Gly
 325 330 335
 Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala Ile
 340 345 350
 Glu Gly Gly Met Ser Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe Asp
 355 360 365
 Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val Ala
 370 375 380
 Gly His Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr Asp
 385 390 395 400
 Leu Ser Thr Thr Ala Leu Glu His Val Leu Leu Phe Ser Leu Gly Ser
 405 410 415
 Cys Asp Leu Pro Glu Ser His Leu Asn Glu Leu Ala Ala Arg Gly Leu
 420 425 430
 Pro Thr Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu Leu
 435 440 445
 Ala Phe Met Thr Leu Val Lys Gln Tyr Gly Pro Glu Phe Val Thr Gly
 450 455 460
 Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Leu Leu Ala Lys Leu Thr
 465 470 475 480
 Asp Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly Arg
 485 490 495

Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys Arg
 500 505 510
 Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly Ile
 515 520 525
 Ile Thr Asp Lys Ile Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val Ala
 530 535 540
 Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp Ile
 545 550 555 560
 Pro Ala Tyr Tyr Ala Ala Gly Pro Ala Gln Arg Gly Val Ile Gly Glu
 565 570 575
 Tyr Cys Ile Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys Phe
 580 585 590
 Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile Asn
 595 600 605
 Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr Cys
 610 615 620
 Leu Leu Arg Leu Ala Asp Gln Lys Gly Phe Ile Leu Pro Asp Thr Gln
 625 630 635 640
 Gly Arg Phe Arg Gly Ala Gly Gly Glu Ala Pro Lys Arg Pro Ala Ala
 645 650 655
 Ala Arg Glu Asp Glu Glu Arg Pro Glu Glu Glu Gly Glu Asp Glu Asp
 660 665 670
 Glu Arg Glu Glu Gly Gly Gly Glu Arg Glu Pro Glu Gly Ala Arg Glu
 675 680 685
 Thr Ala Gly Arg His Val Gly Tyr Gln Gly Ala Arg Val Leu Asp Pro
 690 695 700
 Thr Ser Gly Phe His Val Asn Pro Val Val Val Phe Asp Phe Ala Ser
 705 710 715 720
 Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu Cys Phe Ser Thr Leu
 725 730 735
 Ser Leu Arg Ala Asp Ala Val Ala His Leu Glu Ala Gly Lys Asp Tyr
 740 745 750
 Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe Phe Val Lys Ala His
 755 760 765
 Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg Asp Trp Leu Ala Met
 770 775 780
 Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Ser Pro Glu Glu Ala
 785 790 795 800
 Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val Cys Asn Ser
 805 810 815
 Val Tyr Gly Phe Thr Gly Val Gln His Gly Leu Leu Pro Cys Leu His

52

Glu Asp Pro Ala Tyr Ala Ile Ala His Gly Val Ala Leu Asn Thr
 1145 1150 1155
 Asp Tyr Tyr Phe Ser His Leu Leu Gly Ala Ala Cys Val Thr Phe
 1160 1165 1170
 Lys Ala Leu Phe Gly Asn Asn Ala Lys Ile Thr Glu Ser Leu Leu
 1175 1180 1185
 Lys Arg Phe Ile Pro Glu Val Trp His Pro Pro Asp Asp Val Ala
 1190 1195 1200
 Ala Arg Leu Arg Ala Ala Gly Phe Gly Ala Val Gly Ala Gly Ala
 1205 1210 1215
 Thr Ala Glu Glu Thr Arg Arg Met Leu His Arg Ala Phe Asp Thr
 1220 1225 1230
 Leu Ala
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<400> 17

Met Phe Ser Gly Gly Gly Gly Pro Leu Ser Pro Gly Gly Lys Ser Ala
 1 5 10 15
 Ala Arg Ala Ala Ser Gly Phe Phe Ala Pro Ala Gly Pro Arg Gly Ala
 20 25 30
 Gly Arg Gly Pro Pro Pro Cys Leu Arg Gln Asn Phe Tyr Asn Pro Tyr
 35 40 45
 Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg
 50 55 60
 His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg
 65 70 75 80
 Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp
 85 90 95
 Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg
 100 105 110
 Asp Val Leu Arg Val Gly Ser Gly Gly Phe Trp Pro Arg Arg Ser Arg
 115 120 125
 Leu Trp Gly Gly Val Asp His Ala Pro Ala Gly Phe Asn Pro Thr Val
 130 135 140
 Thr Val Phe His Val Tyr Asp Ile Leu Glu Asn Val Glu His Ala Tyr
 145 150 155 160
 Gly Met Arg Ala Ala Gln Phe His Ala Arg Phe Met Asp Ala Ile Thr
 165 170 175
 Pro Thr Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly His

180					185					190					
Arg	Val	Ala	Val	His	Val	Tyr	Gly	Thr	Arg	Gln	Tyr	Phe	Tyr	Met	Asn
		195					200					205			
Lys	Glu	Glu	Val	Asp	Arg	His	Leu	Gln	Cys	Arg	Ala	Pro	Arg	Asp	Leu
	210					215					220				
Cys	Glu	Arg	Met	Ala	Ala	Ala	Leu	Arg	Glu	Ser	Pro	Gly	Ala	Ser	Phe
225					230					235					240
Arg	Gly	Ile	Ser	Ala	Asp	His	Phe	Glu	Ala	Glu	Val	Val	Glu	Arg	Thr
				245					250					255	
Asp	Val	Tyr	Tyr	Tyr	Glu	Thr	Arg	Pro	Ala	Leu	Phe	Tyr	Arg	Val	Tyr
			260					265					270		
Val	Arg	Ser	Gly	Arg	Val	Leu	Ser	Tyr	Leu	Cys	Asp	Asn	Phe	Cys	Pro
		275					280					285			
Ala	Ile	Lys	Lys	Tyr	Glu	Gly	Gly	Val	Asp	Ala	Thr	Thr	Arg	Phe	Ile
	290					295					300				
Leu	Asp	Asn	Pro	Gly	Phe	Val	Thr	Phe	Gly	Trp	Tyr	Arg	Leu	Lys	Pro
305					310					315					320
Gly	Arg	Asn	Asn	Thr	Leu	Ala	Gln	Pro	Arg	Ala	Pro	Met	Ala	Phe	Gly
				325					330					335	
Thr	Ser	Ser	Asp	Val	Glu	Phe	Asn	Cys	Thr	Ala	Asp	Asn	Leu	Ala	Ile
			340					345					350		
Glu	Gly	Gly	Met	Ser	Asp	Leu	Pro	Ala	Tyr	Lys	Leu	Met	Cys	Phe	Asp
		355					360					365			
Ile	Glu	Cys	Lys	Ala	Gly	Gly	Glu	Asp	Glu	Leu	Ala	Phe	Pro	Val	Ala
	370					375					380				
Gly	His	Pro	Glu	Asp	Leu	Val	Ile	Gln	Ile	Ser	Cys	Leu	Leu	Tyr	Asp
385					390					395					400
Leu	Ser	Thr	Thr	Ala	Leu	Glu	His	Val	Leu	Leu	Phe	Ser	Leu	Gly	Ser
				405					410					415	
Cys	Asp	Leu	Pro	Glu	Ser	His	Leu	Asn	Glu	Leu	Ala	Ala	Arg	Gly	Leu
			420					425					430		
Pro	Thr	Pro	Val	Val	Leu	Glu	Phe	Asp	Ser	Glu	Phe	Glu	Met	Leu	Leu
		435					440					445			
Ala	Phe	Met	Thr	Leu	Val	Lys	Gln	Tyr	Gly	Pro	Glu	Phe	Val	Thr	Gly
	450					455					460				
Tyr	Asn	Ile	Ile	Asn	Phe	Asp	Trp	Pro	Phe	Leu	Leu	Ala	Lys	Leu	Thr
465					470					475					480
Asp	Ile	Tyr	Lys	Val	Pro	Leu	Asp	Gly	Tyr	Gly	Arg	Met	Asn	Gly	Arg
				485					490					495	
Gly	Val	Phe	Arg	Val	Trp	Asp	Ile	Gly	Gln	Ser	His	Phe	Gln	Lys	Arg
			500					505					510		

Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly Ile
 515 520 525
 Ile Thr Asp Lys Ile Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val Ala
 530 535 540
 Glu Ala Val Leu Lys Asp Lys Lys Lys Asp Leu Ser Tyr Arg Asp Ile
 545 550 555 560
 Pro Ala Tyr Tyr Ala Ala Gly Pro Ala Gln Arg Gly Val Ile Gly Glu
 565 570 575
 Tyr Cys Ile Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys Phe
 580 585 590
 Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile Asn
 595 600 605
 Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr Cys
 610 615 620
 Leu Leu Arg Leu Ala Asp Gln Lys Gly Phe Ile Leu Pro Asp Thr Gln
 625 630 635 640
 Gly Arg Phe Arg Gly Ala Gly Gly Glu Ala Pro Lys Arg Pro Ala Ala
 645 650 655
 Ala Arg Glu Asp Glu Glu Arg Pro Glu Glu Glu Gly Glu Asp Glu Asp
 660 665 670
 Glu Arg Glu Glu Gly Gly Gly Glu Arg Glu Pro Glu Gly Ala Arg Glu
 675 680 685
 Thr Ala Gly Arg His Val Gly Tyr Gln Gly Ala Arg Val Leu Asp Pro
 690 695 700
 Ile Ser Gly Phe His Val Asn Pro Val Val Val Phe Asp Phe Ala Ser
 705 710 715 720
 Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu Cys Phe Ser Thr Leu
 725 730 735
 Ser Leu Arg Ala Asp Ala Val Ala His Leu Glu Ala Gly Lys Asp Tyr
 740 745 750
 Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe Phe Val Lys Ala His
 755 760 765
 Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg Asp Trp Leu Ala Met
 770 775 780
 Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Ser Pro Glu Glu Ala
 785 790 795 800
 Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val Cys Asn Ser
 805 810 815
 Val Tyr Gly Phe Thr Gly Val Gln His Gly Leu Leu Pro Cys Leu His
 820 825 830
 Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu Met Leu Leu Ala Thr
 835 840 845

Arg Glu Tyr Val His Ala Arg Trp Ala Ala Phe Glu Gln Leu Leu Ala
 850 855 860
 Asp Phe Pro Glu Ala Ala Asp Met Arg Ala Pro Gly Pro Tyr Ser Met
 865 870 875 880
 Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu Cys Arg Gly
 885 890 895
 Leu Thr Ala Ala Gly Leu Thr Ala Met Gly Asp Lys Met Ala Ser His
 900 905 910
 Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys Leu Glu Cys Glu Lys
 915 920 925
 Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys Lys Tyr Ile Gly Val
 930 935 940
 Ile Tyr Gly Gly Lys Met Leu Ile Lys Gly Val Asp Leu Val Arg Lys
 945 950 955 960
 Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg Ala Leu Val Asp Leu
 965 970 975
 Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala Ala Ala Leu Ala Glu
 980 985 990
 Arg Pro Ala Glu Glu Trp Leu Ala Arg Pro Leu Pro Glu Gly Leu Gln
 995 1000 1005
 Ala Phe Gly Ala Val Leu Val Asp Ala His Arg Arg Ile Thr Asp
 1010 1015 1020
 Pro Glu Arg Asp Ile Gln Asp Phe Val Leu Thr Ala Glu Leu Ser
 1025 1030 1035
 Arg His Pro Arg Ala Tyr Thr Asn Lys Arg Leu Ala His Leu Thr
 1040 1045 1050
 Val Tyr Tyr Lys Leu Met Ala Arg Arg Ala Gln Val Pro Ser Ile
 1055 1060 1065
 Lys Asp Arg Ile Pro Tyr Val Ile Val Ala Gln Thr Arg Glu Val
 1070 1075 1080
 Glu Glu Thr Val Ala Arg Leu Ala Ala Leu Arg Glu Leu Asp Ala
 1085 1090 1095
 Ala Ala Pro Gly Asp Glu Pro Ala Pro Pro Ala Ala Leu Pro Ser
 1100 1105 1110
 Pro Ala Lys Arg Pro Arg Glu Thr Pro Ser Pro Ala Asp Pro Pro
 1115 1120 1125
 Gly Gly Ala Ser Lys Pro Arg Lys Leu Leu Val Ser Glu Leu Ala
 1130 1135 1140
 Glu Asp Pro Ala Tyr Ala Ile Ala His Gly Val Ala Leu Asn Thr
 1145 1150 1155
 Asp Tyr Tyr Phe Ser His Leu Leu Gly Ala Ala Cys Val Thr Phe

1160	1165	1170
Lys Ala Leu Phe Gly Asn Asn	Ala Lys Ile Thr Glu Ser Leu Leu	
1175	1180	1185
Lys Arg Phe Ile Pro Glu Val	Trp His Pro Pro Asp Asp Val Thr	
1190	1195	1200
Ala Arg Leu Arg Ala Ala Gly	Phe Gly Ala Val Gly Ala Gly Ala	
1205	1210	1215
Thr Ala Glu Glu Thr Arg Arg	Met Leu His Arg Ala Phe Asp Thr	
1220	1225	1230
Leu Ala		
1235		
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Met Phe Ser Gly Gly Gly Gly Pro Leu Ser Pro Gly Gly Lys Ser Ala		
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Ala Arg Ala Ala Ser Gly Phe Phe Ala Pro Ala Gly Pro Arg Gly Ala		
20 25 30		
Gly Arg Gly Pro Pro Pro Cys Leu Arg Gln Asn Phe Tyr Asn Pro Tyr		
35 40 45		
Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg		
50 55 60		
His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg		
65 70 75 80		
Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp		
85 90 95		
Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg		
100 105 110		
Asp Val Leu Arg Val Gly Ser Gly Gly Phe Trp Pro Arg Arg Ser Arg		
115 120 125		
Leu Trp Gly Gly Val Asp His Ala Pro Ala Gly Phe Asn Pro Thr Val		
130 135 140		
Thr Val Phe His Val Tyr Asp Ile Leu Glu Asn Val Glu His Ala Tyr		
145 150 155 160		
Gly Met Arg Ala Ala Gln Phe His Ala Arg Phe Met Asp Ala Ile Thr		
165 170 175		
Pro Thr Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly His		
180 185 190		
Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met Asn		
195 200 205		

Lys Glu Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp Leu
 210 215 220
 Cys Glu Arg Met Ala Ala Ala Leu Arg Glu Ser Pro Gly Ala Ser Phe
 225 230 235 240
 Arg Gly Ile Ser Ala Asp His Phe Glu Ala Glu Val Val Glu Arg Thr
 245 250 255
 Asp Val Tyr Tyr Tyr Glu Thr Arg Pro Ala Leu Phe Tyr Arg Val Tyr
 260 265 270
 Val Arg Ser Gly Arg Val Leu Ser Tyr Leu Cys Asp Asn Phe Cys Pro
 275 280 285
 Ala Ile Lys Lys Tyr Glu Gly Gly Val Asp Ala Thr Thr Arg Phe Ile
 290 295 300
 Leu Asp Asn Pro Gly Phe Val Thr Phe Gly Trp Tyr Arg Leu Lys Pro
 305 310 315 320
 Gly Arg Asn Asn Thr Leu Ala Gln Pro Arg Ala Pro Met Ala Phe Gly
 325 330 335
 Thr Ser Ser Asp Val Glu Phe Asn Cys Thr Ala Asp Asn Leu Ala Ile
 340 345 350
 Glu Gly Gly Met Ser Asp Leu Pro Ala Tyr Lys Leu Met Cys Phe Asp
 355 360 365
 Ile Glu Cys Lys Ala Gly Gly Glu Asp Glu Leu Ala Phe Pro Val Ala
 370 375 380
 Gly His Pro Glu Asp Leu Val Ile Gln Ile Ser Cys Leu Leu Tyr Asp
 385 390 395 400
 Leu Ser Thr Thr Ala Leu Glu His Val Leu Leu Phe Ser Leu Gly Ser
 405 410 415
 Cys Asp Leu Pro Glu Ser His Leu Asn Glu Leu Ala Ala Arg Gly Leu
 420 425 430
 Pro Thr Pro Val Val Leu Glu Phe Asp Ser Glu Phe Glu Met Leu Leu
 435 440 445
 Ala Phe Met Thr Leu Val Lys Gln Tyr Gly Pro Glu Phe Val Thr Gly
 450 455 460
 Tyr Asn Ile Ile Asn Phe Asp Trp Pro Phe Leu Leu Ala Lys Leu Thr
 465 470 475 480
 Asp Ile Tyr Lys Val Pro Leu Asp Gly Tyr Gly Arg Met Asn Gly Arg
 485 490 495
 Gly Val Phe Arg Val Trp Asp Ile Gly Gln Ser His Phe Gln Lys Arg
 500 505 510
 Ser Lys Ile Lys Val Asn Gly Met Val Asn Ile Asp Met Tyr Gly Ile
 515 520 525
 Ile Thr Asp Lys Ile Lys Leu Ser Ser Tyr Lys Leu Asn Ala Val Ala

530				535				540							
Glu 545	Ala	Val	Leu	Lys	Asp 550	Lys	Lys	Lys	Asp	Leu 555	Ser	Tyr	Arg	Asp	Ile 560
Pro	Thr	Tyr	Tyr	Ala 565	Ala	Gly	Pro	Ala	Gln 570	Arg	Gly	Val	Ile	Gly 575	Glu
Tyr	Cys	Ile	Gln 580	Asp	Ser	Leu	Leu	Val 585	Gly	Gln	Leu	Phe	Phe 590	Lys	Phe
Leu	Pro	His 595	Leu	Glu	Leu	Ser	Ala 600	Val	Ala	Arg	Leu	Ala 605	Gly	Ile	Asn
Ile	Thr 610	Arg	Thr	Ile	Tyr	Asp 615	Gly	Gln	Gln	Ile	Arg 620	Val	Phe	Thr	Cys
Leu 625	Leu	Arg	Leu	Ala	Asp 630	Gln	Lys	Gly	Phe	Ile 635	Leu	Pro	Asp	Thr	Gln 640
Gly	Arg	Phe	Arg	Gly 645	Ala	Gly	Gly	Glu	Ala 650	Pro	Lys	Arg	Pro	Ala 655	Ala
Ala	Arg	Glu	Asp 660	Glu	Glu	Arg	Pro	Glu 665	Glu	Glu	Gly	Glu	Asp 670	Glu	Asn
Glu	Arg	Glu 675	Glu	Gly	Gly	Gly	Glu 680	Arg	Glu	Pro	Glu	Gly 685	Ala	Arg	Glu
Thr 690	Ala	Gly	Arg	His	Val	Gly 695	Tyr	Gln	Gly	Ala 700	Arg	Val	Leu	Asp	Pro
Thr 705	Ser	Gly	Phe	His	Val 710	Asn	Pro	Val	Val	Val 715	Phe	Asp	Phe	Ala	Ser 720
Leu	Tyr	Pro	Ser	Ile 725	Ile	Gln	Ala	His	Asn 730	Leu	Cys	Phe	Ser	Thr 735	Leu
Ser	Leu	Arg	Ala 740	Asp	Ala	Val	Ala 745	His	Leu	Glu	Ala	Gly 750	Lys	Asp	Tyr
Leu	Glu 755	Ile	Glu	Val	Gly	Gly	Arg 760	Arg	Leu	Phe	Phe	Val 765	Lys	Ala	His
Val 770	Arg	Glu	Ser	Leu	Leu	Ser 775	Ile	Leu	Leu	Arg	Asp 780	Trp	Leu	Ala	Met
Arg 785	Lys	Gln	Ile	Arg	Ser 790	Arg	Ile	Pro	Gln 795	Ser	Ser	Pro	Glu	Glu	Ala 800
Val	Leu	Leu	Asp 805	Lys	Gln	Gln	Ala	Ala	Ile 810	Lys	Val	Val	Cys	Asn 815	Ser
Val	Tyr	Gly	Phe 820	Thr	Gly	Val	Gln	His 825	Gly	Leu	Leu	Pro	Cys 830	Leu	His
Val	Ala 835	Ala	Thr	Val	Thr	Thr	Ile 840	Gly	Arg	Glu	Met 845	Leu	Leu	Ala	Thr
Arg 850	Glu	Tyr	Val	His	Ala	Arg 855	Trp	Ala	Ala	Phe	Glu 860	Gln	Leu	Leu	Ala

Asp Phe Pro Glu Ala Ala Asp Met Arg Ala Pro Gly Pro Tyr Ser Met
 865 870 875 880
 Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu Cys Arg Gly
 885 890 895
 Leu Thr Ala Ala Gly Leu Thr Ala Val Gly Asp Lys Met Ala Ser His
 900 905 910
 Ile Ser Arg Ala Leu Phe Leu Pro Pro Ile Lys Leu Glu Cys Glu Lys
 915 920 925
 Thr Phe Thr Lys Leu Leu Leu Ile Ala Lys Lys Lys Tyr Ile Gly Val
 930 935 940
 Ile Tyr Gly Gly Lys Met Leu Ile Lys Gly Val Asp Leu Val Arg Lys
 945 950 955 960
 Asn Asn Cys Ala Phe Ile Asn Arg Thr Ser Arg Ala Leu Val Asp Leu
 965 970 975
 Leu Phe Tyr Asp Asp Thr Val Ser Gly Ala Ala Ala Ala Leu Ala Glu
 980 985 990
 Arg Pro Ala Glu Glu Trp Leu Ala Arg Pro Leu Pro Glu Gly Leu Gln
 995 1000 1005
 Ala Phe Gly Ala Val Leu Val Asp Ala His Arg Arg Ile Thr Asp
 1010 1015 1020
 Pro Glu Arg Asp Ile Gln Asp Phe Val Leu Thr Ala Glu Leu Ser
 1025 1030 1035
 Arg His Pro Arg Ala Tyr Thr Asn Lys Arg Leu Ala His Leu Thr
 1040 1045 1050
 Val Tyr Tyr Lys Leu Met Ala Arg Arg Ala Gln Val Pro Ser Ile
 1055 1060 1065
 Lys Asp Arg Ile Pro Tyr Val Ile Val Ala Gln Thr Arg Glu Val
 1070 1075 1080
 Glu Glu Thr Val Ala Arg Leu Ala Ala Leu Arg Glu Leu Asp Ala
 1085 1090 1095
 Ala Ala Pro Gly Asp Glu Pro Ala Pro Pro Ala Ala Leu Pro Ser
 1100 1105 1110
 Pro Ala Lys Arg Pro Arg Glu Thr Pro Ser Pro Ala Asp Pro Pro
 1115 1120 1125
 Gly Gly Ala Ser Lys Pro Arg Lys Leu Leu Val Ser Glu Leu Ala
 1130 1135 1140
 Glu Asp Pro Ala Tyr Ala Ile Ala His Gly Val Ala Leu Asn Thr
 1145 1150 1155
 Asp Tyr Tyr Phe Ser His Leu Leu Gly Ala Ala Cys Val Thr Phe
 1160 1165 1170
 Lys Ala Leu Phe Gly Asn Asn Ala Lys Ile Thr Glu Ser Leu Leu
 1175 1180 1185

Lys Arg Phe Ile Pro Glu Val Trp His Pro Pro Asp Asp Val Ala
 1190 1195 1200

Ala Arg Leu Arg Thr Ala Gly Phe Gly Ala Val Gly Ala Gly Ala
 1205 1210 1215

Thr Ala Glu Glu Thr Arg Arg Met Leu His Arg Ala Phe Asp Thr
 1220 1225 1230

Leu Ala
 1235

<210> 19
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Met Phe Ser Gly Gly Gly Gly Pro Leu Ser Pro Gly Gly Lys Ser Ala
 1 5 10 15

Ala Arg Ala Ala Ser Gly Phe Phe Ala Pro Ala Gly Pro Arg Gly Ala
 20 25 30

Gly Arg Gly Pro Pro Pro Cys Leu Arg Gln Asn Phe Tyr Asn Pro Tyr
 35 40 45

Leu Ala Pro Val Gly Thr Gln Gln Lys Pro Thr Gly Pro Thr Gln Arg
 50 55 60

His Thr Tyr Tyr Ser Glu Cys Asp Glu Phe Arg Phe Ile Ala Pro Arg
 65 70 75 80

Val Leu Asp Glu Asp Ala Pro Pro Glu Lys Arg Ala Gly Val His Asp
 85 90 95

Gly His Leu Lys Arg Ala Pro Lys Val Tyr Cys Gly Gly Asp Glu Arg
 100 105 110

Asp Val Leu Arg Val Gly Ser Gly Gly Phe Trp Pro Arg Arg Ser Arg
 115 120 125

Leu Trp Gly Gly Val Asp His Ala Pro Ala Gly Phe Asn Pro Thr Val
 130 135 140

Thr Val Phe His Val Tyr Asp Ile Leu Glu Asn Val Glu His Ala Tyr
 145 150 155 160

Gly Met Arg Ala Ala Gln Phe His Ala Arg Phe Met Asp Ala Ile Thr
 165 170 175

Pro Thr Gly Thr Val Ile Thr Leu Leu Gly Leu Thr Pro Glu Gly His
 180 185 190

Arg Val Ala Val His Val Tyr Gly Thr Arg Gln Tyr Phe Tyr Met Asn
 195 200 205

Lys Glu Glu Val Asp Arg His Leu Gln Cys Arg Ala Pro Arg Asp Leu
 210 215 220

Cys	Glu	Arg	Met	Ala	Ala	Ala	Leu	Arg	Glu	Ser	Pro	Gly	Ala	Ser	Phe	225	230	235	240
Arg	Gly	Ile	Ser	Ala	Asp	His	Phe	Glu	Ala	Glu	Val	Val	Glu	Arg	Thr	245	250	255	
Asp	Val	Tyr	Tyr	Tyr	Glu	Thr	Arg	Pro	Ala	Leu	Phe	Tyr	Arg	Val	Tyr	260	265	270	
Val	Arg	Ser	Gly	Arg	Val	Leu	Ser	Tyr	Leu	Cys	Asp	Asn	Phe	Cys	Pro	275	280	285	
Ala	Ile	Lys	Lys	Tyr	Glu	Gly	Gly	Val	Asp	Ala	Thr	Thr	Arg	Phe	Ile	290	295	300	
Leu	Asp	Asn	Pro	Gly	Phe	Val	Thr	Phe	Gly	Trp	Tyr	Arg	Leu	Lys	Pro	305	310	315	320
Gly	Arg	Asn	Asn	Thr	Leu	Ala	Gln	Pro	Arg	Ala	Pro	Met	Ala	Phe	Gly	325	330	335	
Thr	Ser	Ser	Asp	Val	Glu	Phe	Asn	Cys	Thr	Ala	Asp	Asn	Leu	Ala	Ile	340	345	350	
Glu	Gly	Gly	Met	Ser	Asp	Leu	Pro	Ala	Tyr	Lys	Leu	Met	Cys	Phe	Asp	355	360	365	
Ile	Glu	Cys	Lys	Ala	Gly	Gly	Glu	Asp	Glu	Leu	Ala	Phe	Pro	Val	Ala	370	375	380	
Gly	His	Pro	Glu	Asp	Leu	Val	Ile	Gln	Ile	Ser	Cys	Leu	Leu	Tyr	Asp	385	390	395	400
Leu	Ser	Thr	Thr	Ala	Leu	Glu	His	Val	Leu	Leu	Phe	Ser	Leu	Gly	Ser	405	410	415	
Cys	Asp	Leu	Pro	Glu	Ser	His	Leu	Asn	Glu	Leu	Ala	Ala	Arg	Gly	Leu	420	425	430	
Pro	Thr	Pro	Val	Val	Leu	Glu	Phe	Asp	Ser	Glu	Phe	Glu	Met	Leu	Leu	435	440	445	
Ala	Phe	Met	Thr	Leu	Val	Lys	Gln	Tyr	Gly	Pro	Glu	Phe	Val	Thr	Gly	450	455	460	
Tyr	Asn	Ile	Ile	Asn	Phe	Asp	Trp	Pro	Phe	Leu	Leu	Ala	Lys	Leu	Thr	465	470	475	480
Asp	Ile	Tyr	Lys	Val	Pro	Leu	Asp	Gly	Tyr	Gly	Arg	Met	Asn	Gly	Arg	485	490	495	
Gly	Val	Phe	Arg	Val	Trp	Asp	Ile	Gly	Gln	Ser	His	Phe	Gln	Lys	Arg	500	505	510	
Ser	Lys	Ile	Lys	Val	Asn	Gly	Met	Val	Asn	Ile	Asp	Met	Tyr	Gly	Ile	515	520	525	
Ile	Thr	Asp	Lys	Ile	Lys	Leu	Ser	Ser	Tyr	Lys	Leu	Asn	Ala	Val	Ala	530	535	540	
Glu	Ala	Val	Leu	Lys	Asp	Lys	Lys	Lys	Asp	Leu	Ser	Tyr	Arg	Asp	Ile	545	550	555	560

Pro Ala Tyr Tyr Ala Ala Gly Pro Ala Gln Arg Gly Val Ile Gly Glu
 565 570 575
 Tyr Cys Ile Gln Asp Ser Leu Leu Val Gly Gln Leu Phe Phe Lys Phe
 580 585 590
 Leu Pro His Leu Glu Leu Ser Ala Val Ala Arg Leu Ala Gly Ile Asn
 595 600 605
 Ile Thr Arg Thr Ile Tyr Asp Gly Gln Gln Ile Arg Val Phe Thr Cys
 610 615 620
 Leu Leu Arg Leu Ala Asp Gln Lys Gly Phe Ile Leu Pro Asp Thr Gln
 625 630 635 640
 Gly Arg Phe Arg Gly Gly Gly Gly Glu Ala Pro Lys Arg Pro Ala Ala
 645 650 655
 Ala Arg Glu Asp Glu Glu Arg Pro Glu Glu Glu Gly Glu Asp Glu Asp
 660 665 670
 Glu Arg Glu Glu Gly Gly Gly Glu Arg Glu Pro Glu Gly Ala Arg Glu
 675 680 685
 Thr Ala Gly Arg His Val Gly Tyr Gln Gly Ala Arg Val Leu Asp Pro
 690 695 700
 Thr Ser Gly Phe His Val Asn Pro Val Val Val Phe Asp Phe Ala Ser
 705 710 715 720
 Leu Tyr Pro Ser Ile Ile Gln Ala His Asn Leu Cys Phe Ser Thr Leu
 725 730 735
 Ser Leu Arg Ala Asp Ala Val Ala His Leu Glu Ala Gly Lys Asp Tyr
 740 745 750
 Leu Glu Ile Glu Val Gly Gly Arg Arg Leu Phe Phe Val Lys Ala His
 755 760 765
 Val Arg Glu Ser Leu Leu Ser Ile Leu Leu Arg Asp Trp Leu Ala Met
 770 775 780
 Arg Lys Gln Ile Arg Ser Arg Ile Pro Gln Ser Ser Pro Glu Glu Ala
 785 790 795 800
 Val Leu Leu Asp Lys Gln Gln Ala Ala Ile Lys Val Val Cys Asn Ser
 805 810 815
 Val Tyr Gly Phe Thr Gly Val Gln His Gly Leu Leu Pro Cys Leu His
 820 825 830
 Val Ala Ala Thr Val Thr Thr Ile Gly Arg Glu Met Leu Leu Ala Thr
 835 840 845
 Arg Glu Tyr Val His Ala Arg Trp Ala Ala Phe Glu Gln Leu Leu Ala
 850 855 860
 Asp Phe Pro Glu Ala Ala Asp Met Arg Ala Pro Gly Pro Tyr Ser Met
 865 870 875 880
 Arg Ile Ile Tyr Gly Asp Thr Asp Ser Ile Phe Val Leu Cys Arg Gly

885					890					895					
Leu	Thr	Ala	Ala	Gly	Leu	Thr	Ala	Val	Gly	Asp	Lys	Met	Ala	Ser	His
			900					905					910		
Ile	Ser	Arg	Ala	Leu	Phe	Leu	Ser	Pro	Ile	Lys	Leu	Glu	Cys	Glu	Lys
		915					920					925			
Thr	Phe	Thr	Lys	Leu	Leu	Leu	Ile	Ala	Lys	Lys	Lys	Tyr	Ile	Gly	Val
		930					935					940			
Ile	Tyr	Gly	Gly	Lys	Met	Leu	Ile	Lys	Gly	Val	Asp	Leu	Val	Arg	Lys
945						950					955				960
Asn	Asn	Cys	Ala	Phe	Ile	Asn	Arg	Thr	Ser	Arg	Ala	Leu	Val	Asp	Leu
				965					970					975	
Leu	Phe	Tyr	Asp	Asp	Thr	Val	Ser	Gly	Ala	Ala	Ala	Ala	Leu	Ala	Glu
			980					985						990	
Arg	Pro	Ala	Glu	Glu	Trp	Leu	Ala	Arg	Pro	Leu	Pro	Glu	Gly	Leu	Gln
		995					1000					1005			
Ala	Phe	Gly	Ala	Val	Leu	Val	Asp	Ala	His	Arg	Arg	Ile	Thr	Asp	
	1010					1015					1020				
Pro	Glu	Arg	Asp	Ile	Gln	Asp	Phe	Val	Leu	Thr	Ala	Glu	Leu	Ser	
	1025					1030					1035				
Arg	His	Pro	Arg	Ala	Tyr	Thr	Asn	Lys	Arg	Leu	Ala	His	Leu	Thr	
	1040					1045					1050				
Val	Tyr	Tyr	Lys	Leu	Met	Ala	Arg	Arg	Ala	Gln	Val	Pro	Ser	Ile	
	1055					1060					1065				
Lys	Asp	Arg	Ile	Pro	Tyr	Val	Ile	Val	Ala	Gln	Thr	Arg	Glu	Val	
	1070					1075					1080				
Glu	Glu	Thr	Val	Ala	Arg	Leu	Ala	Ala	Leu	Arg	Glu	Leu	Asp	Ala	
	1085					1090					1095				
Ala	Ala	Pro	Gly	Asp	Glu	Pro	Ala	Pro	Pro	Ala	Ala	Leu	Pro	Ser	
	1100					1105					1110				
Pro	Ala	Lys	Arg	Pro	Arg	Glu	Thr	Pro	Leu	His	Ala	Asp	Pro	Pro	
	1115					1120					1125				
Gly	Gly	Ala	Ser	Lys	Pro	Arg	Lys	Leu	Leu	Val	Ser	Glu	Leu	Ala	
	1130					1135					1140				
Glu	Asp	Pro	Ala	Tyr	Ala	Ile	Ala	His	Gly	Val	Ala	Leu	Asn	Thr	
	1145					1150					1155				
Asp	Tyr	Tyr	Phe	Ser	His	Leu	Leu	Gly	Ala	Ala	Cys	Val	Thr	Phe	
	1160					1165					1170				
Lys	Ala	Leu	Phe	Gly	Asn	Asn	Ala	Lys	Ile	Thr	Glu	Ser	Leu	Leu	
	1175					1180					1185				
Lys	Arg	Phe	Ile	Pro	Glu	Val	Trp	His	Pro	Pro	Asp	Asp	Val	Ala	
	1190					1195					1200				

Ala	Arg	Leu	Arg	Ala	Ala	Gly	Phe	Gly	Ala	Val	Gly	Ala	Gly	Ala
1205						1210					1215			
Thr	Ala	Glu	Glu	Thr	Arg	Arg	Met	Leu	His	Arg	Ala	Phe	Asp	Thr
1220						1225					1230			
Leu	Ala													
1235														

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(54) Title: A METHOD FOR TREATING HERPES VIRUSES

(57) Abstract: The present invention relates to a method for selecting an anti-herpes viral compound and a method for selectively inhibiting herpesvirus in a human host in need of such treatment. The present invention relates to a method for selecting an anti-herpes viral compound and a method for selectively inhibiting herpesvirus in a human host in need of such treatment.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/16525

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 G01N33/569 A61P31/22 C07K14/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 097 633 A (SUNDQVIST VIVI ANNE ;WAHREN BRITTA (SE); HARMENBERG JOHAN (SE)) 4 January 1984 (1984-01-04) the whole document	1,2,4,5, 8,9,11, 12,16, 17,20, 23-26
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/16525

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, A	WO 00 40563 A (STROHBACH JOSEPH WALTER ; SCOTT ALLEN (US); UPJOHN CO (US); SCHNUTE) 13 July 2000 (2000-07-13) abstract -----	1, 2, 4, 5, 8, 9, 11, 12, 16, 17, 20, 23-26
P, A	WO 00 40561 A (STROHBACH JOSEPH WALTER ; UPJOHN CO (US); SCHNUTE MARK E (US); THAI) 13 July 2000 (2000-07-13) abstract -----	1, 2, 4, 5, 8, 9, 11, 12, 16, 17, 20, 23-26
A	WO 94 24296 A (UNIV SASKATCHEWAN) 27 October 1994 (1994-10-27) abstract -----	25, 26

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/16525

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 23 and 24 relate to a compound defined by reference to a desirable characteristic or property, namely the change of the wild type HSV-1 polymerases at amino acid 823 from valine to alanine in the presence of said compound.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds 1-17 in figure 1.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/16525

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